BRAIN

VOL. 81, PART 4.

# THE PROGNOSTIC VALUE OF THE MUSCLE BIOPSY IN THE "FLOPPY INFANT"[1]

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## DEFINITION OF TERMS

FROM the historical survey below, one can see that the clinical differentiation of these various diseases is not always clear. The definition of these terms rests, frequently, upon the time of origin, the progress, and certain small specific clinical variances between the five disorders to be described herein. The authors use the following terminology:

(1) Infantile Spinal Muscular Atrophy (Werdnig-Hoffmann's Disease) is characterized by a progressive wasting of skeletal muscle, almost always proximal, with onset usually within the first year of life. The wasting of muscle in this disease appears to be secondary to denervation.

The age of onset is usually within the first year of life. It may be on or about the natal period. The youngest case in the present series was examined at 28 days of age. The onset of muscular weakness in a previously healthy infant should, however, suggest this diagnosis above all others listed herein.

Fasciculatory movements in the tongue, and/or involvement of pharyngeal and laryngeal musculature should raise the index of suspicion of this disorder. Wasting of limb and trunk muscles may not be obvious owing to normal infantile adiposity (fig. 1, Plate LIX). X-rays for soft tissues (fig. 2), however, will reveal, in the majority of cases, profound muscular wasting. The disease is characteristically progressive, but may be slowly so, the oldest patient of this series being 31 years of age. The majority, however,

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die from intercurrent disease within the first four years of life. Remissions of two or more years are not uncommon, and the child may actually seem to improve, as in the case of C. E. The ultimate outcome, however, has in our experience always been fatal. The weakness in this disorder differs from most other neuropathic disorders of muscle in that it is primarily proximal. Respirations may be an important clue in that there may be a marked dissociation of respiratory movements. Thus, respiration may be markedly diaphragmatic with a paradoxical narrowing of the chest on inspiration, or it may be pectoral, with the child using his shoulder muscles as ancillary means of increasing the chest capacity on inspiration. Such dissociated respiratory movements are uncommon in the other disorders listed below.

Contractures are generally proportional to the length of the illness, being extremely uncommon in the first few years of the illness, but becoming more common as the illness progresses. As infantile adiposity is lost, fascicular movements may be seen in the limb muscles. The electromyogram may be of use in only a small percentage of these cases, in our experience, within the first year, fibrillary activity being most marked after the third year. The occasional spontaneous potential of one to two milliseconds and of 50 microvolts, or less, is not necessarily pathognomonic of denervation. Reflexes are generally diminished or absent. Biopsy studies demonstrate the characteristic picture of large groups of small fibres, singly or in groups, among which normally sized or slightly hypertrophic fibres are seen. Such studies will be described in detail.

(2) By the term "Benign Congenital Hypotonia," the authors wish to delineate a group of infants with weakness of somatic musculature again more prominent in the proximal group, which characteristically improved in time and in whose muscles our biopsies show no structural abnormality. In the initial stages, intelligence testing may demonstrate some defect which lies predominantly in performance; these defects usually disappear as the patient improves. Fasciculations are not seen in these children; there is no profound atrophy or wasting; reflexes may, however, be depressed; respiration is rarely affected. Such patients, however, may die from intercurrent infection, as did Spiller's.

Electromyography reveals a quiescent muscle in the cases reported, with no spontaneous activity. These cases correspond to those described first by Oppenheim (1900), subsequently by Haushalter (1920), Sobel (1926), Brandt (1950), and finally Walton (1956*b*), who has used the title of Benign Congenital Hypotonia. Biopsy in such cases reveals either normal muscle, or universally small fibres for the age of the patient.

(3) The problem of *congenital or infantile muscular dystrophy*, as seen in the discussion of the literature below, has been the most difficult. We feel the diagnosis of this disease must rest on the pathology of the muscle, and few cases in the literature satisfy this criterion. Clinically,

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such cases show a progressive proximal muscular weakness, present on or soon after birth, progressing with varying rates but often slowly. A certain proportion are familial. Involvement of pharyngeal or laryngeal musculature should raise a question as to the diagnosis, as should fasciculations within the tongue or elsewhere. Reflexes are generally depressed or absent. As the child grows, there is an algebraic relation between the normal somatic growth of the child, and the progress of the disease, so that for periods of time the disease may seem arrested, or the child may even seem to improve. On the other hand, if the disease is progressing rapidly, the converse may be true. Respiration is generally affected last, with equal involvement of intercostals, diaphragm, and shoulder muscles. Here also the electromyogram may demonstrate some spontaneous activity. Soft tissue X-rays again may be useful in demonstrating severe wasting which would differentiate this disorder from the benign congenital hypotonia. The pathological picture of a biopsy in such cases differs from infantile spinal atrophy in showing: (1) Excess of endomysial collagen and adipose tissue; (2) Disappearance of small fibres, leaving groups or isolated large and medium-sized fibres in a sea of adipose or collagenous tissue; (3) Structural changes in larger fibres will lose their architecture and undergo fragmentation and phagocytosis; (4) Areas of inflammation, and (5) Areas of regeneration. It would appear that the amount of phagocytosis, inflammation, and regeneration are in direct correlation with the rapidity of the disease at the time of biopsy.

(4) The "Central Core" disease (Shy and Magee, 1956) differs both from infantile spinal atrophy, and infantile muscular dystrophy, which are progressive; and from infantile benign hypotonia, which improves. In this unusual family there is a characteristic and quite pathognomonic alteration in the muscle fibre. In these patients also there is proximal muscle weakness from birth. Walking, sitting, and climbing stairs are delayed. In the 5 cases so reported, however, all patients were able, ultimately, to be ambulatory, but never gained full power of proximal muscles, so that there was a life-long difficulty of climbing stairs, running, and sitting, and a waddling gait. These disabilities were, however, non-progressive. Reflexes in this peculiar family were also present and quite active. Musculature innervated by the cranial nerves, was spared. Involuntary movement of muscle fascicles was not observed. The electromyogram demonstrated a muscle that was quiet at rest, with normal potentials on volition.

(5) To be clinically precise, the last group to be discussed would not fall under the title of the prognosis of biopsy of the hypotonic infant, in that such infants generally may have but limited hypotonicity, but always have joint deformity or muscle contracture at the time of birth. This group has been characteristically called arthrogryposis by Löwenthal (1954), Middleton (1934), Banker *et al.* (1957). Both neuropathic and myopathic

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changes have been described in this disorder. The natural history of this disease is not clearly defined in the majority of medical textbooks. One receives the impression that most of these children ultimately progressed to complete invalidism. The pathology in such cases, from biopsy specimens, may become exceedingly complex. If one accepts the presence of peripheral fibrils, central vesicular nuclei with prominent nucleoli, combined with basophilism, as characteristic of fœtal muscle, this is the disorder in which this picture may frequently be found. In addition to this, however, Adams *et al.* (1953) have described a case in which a neuropathy was found.

## Historical Survey

The confusion in which the nosology of infantile muscular hypotonia has remained for more than fifty years derives from controversies which were ripe during the early years of the present century. At that time, three different views as to the possible histopathology and patho-physiology of this condition were held by (1) Werdnig (1891) and Hoffmann (1893), (2) Oppenheim (1900), and (3) Batten (1903). As two of these theories were without pathological confirmation, and as there might be no valid differences in symptomatology between the three forms in the early stages, the choice of diagnosis in individual cases inevitably became governed by caprice more than by evidence. This subject has been very fully reviewed by Brandt (1950), but a short epitome of the literature may be permitted.

(1) *Progressive infantile muscular atrophy.*—Werdnig (1891) and Hoffmann (1893, 1897, 1900*a*) described, under the title of "hereditary progressive spinal muscular atrophy in childhood," a condition of muscular flaccidity and weakness coming on after a few weeks or months of normal post-partum development, and progressing during the next few months to paralysis which involved the chest and trunk as well as the proximal limb muscles. Paralysis of deglutition often appeared before death, which was rarely delayed beyond the 4th year of life. Post-mortem examination in fatal cases showed reduction in number of ventral horn cells, especially in the cervical and lumbosacral enlargements or the spinal cord with shrinkage or degeneration of some of the remainder and a corresponding loss of size and of myelin stained in the ventral roots. The appearances of the muscles were those of a neuropathic atrophy. Although in none of their cases was weakness apparent at birth or during the first weeks of life, a congenital case with similar pathological findings was described by Beevor (1902).

(2) *Amyotonia congenita.*—In 1900 and 1904 Oppenheim described, under the name "myotonia congenita", a condition of general or local hypotonia of muscles in early infancy, with no wasting of muscles, but great weakness often amounting to apparent paralysis of the limbs. As described by him in 1904, the legs were always affected, sometimes

also the arms. Much less often the muscles of the trunk and neck. The muscles supplied by the cranial nerves were always spared. The tendon reflexes were greatly diminished or lost and the electrical excitabilityof the affected muscles was equally weak or absent. Oppenheim considered that this condition was capable of gradual improvement, but (1904) recovery might be incomplete, and in the 1908 edition of his texbook (English translation, 1911) he makes no mention of complete recovery. Later, to avoid confusion, the name was generally changed to "Amyotonia congenita."

Oppenheim considered that the muscular weakness and atony were due to delayed development of muscles, but he did not exclude the possibility of a similar delay in the maturation of the ventral horn cells *or of their functions*. Although by 1908 he had only collected "8 or 9" cases of this disease in his clinic, the prestige of his name made this diagnosis popular for all forms of congenital muscular hypotonia, and this diagnosis was given both in his own clinic and in England, France, and America, to many cases which progressed to a fatal issue, and in which post-mortem examination revealed the lesions described by Werdnig and Hoffmann. In reviewing post-mortem records of cases published under the diagnosis of Oppenheim's disease, Greenfield and Stern (1927) found only one case in which the changes in the muscles were not those of a neuropathic atrophy. This case, reported by Spiller (1904-5), concerned a boy who appeared to be mentally retarded. His mother noticed that when 5 months old he did not take notice of things as he should, and the report states that shortly before his death at 23 months, "he seemed at times to notice a watch held before his eyes." He could not be fed with a spoon and his death was accelerated by malnutrition. In an otherwise negative post-mortem examination, the muscles were seen to be small, pale and hyaloid, and microscopically contained only fibres of small calibre; but no measurements were given and the appearances were not illustrated.

Hoffmann is quoted by Slauck (1921) as writing, shortly before his death, "Myotonia is not a special form of progressive spinal muscular atrophy, but is the disease itself."

(3) *Congenital muscular dystrophy*.—Batten (1903, 1910, 1911*b*, 1917), while recognizing the Werdnig-Hoffmann disease, considered that the condition described by Oppenheim was a congenital form of muscular dystrophy which he called (1910) the "simple atrophic type." This might be present at birth or appear in early infancy. All the muscles were small and weak but all movements could be feebly performed. The condition was slowly progressive. The children might become able to sit up, or possibly to stand with support, but rarely learned to walk. Contractures tended to appear later in the disease. Some cases were familial. In Silvestri's (1909) case, in which a pathological examination was not made, other members of the family developed typical muscular dystrophy at

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later age periods. This conception of a congenital type of muscular dystrophy was not widely accepted although a few cases were reported under this diagnosis. Unfortunately, the lesions in the muscles in several such cases differed in no respect from those constantly found in the Werdnig-Hoffmann disease, although the author found little evidence of disease in the spinal cord.

Therefore, although the great majority of pathological examinations in cases of muscular hypotonia beginning in early infancy showed the lesions of anterior horn cells and nerve roots described by Werdnig and Hoffmann, there remained the possibility that severe infantile hypotonia might also be due either to primary muscular dystrophy or to slow maturation, either of the muscles, the motor neurones or their nerve endings. Two cases reported by Haushalter (1920) supported these possibilities. His Case 2 was that of a girl of 11 years at the time of publication. In an otherwise normal pregnancy, fœtal movements were not felt till the 6th month. The child was slightly cyanosed at birth, and remained limp and inert, but sucked well. The limbs were thin and could be placed in any position. This condition continued with little change until the age of 4 years, when she was still unable to support her weight in standing. She first walked at 2 years, but was almost unintelligible until the age of 4. Thereafter there was great improvement: She rapidly learned to talk and to walk; at 7 years of age she went to school and at 11 years was up to the general level of her class. She could walk and run, but her limbs were still lax. This case, therefore, corresponded clinically to Oppenheim's conception of amyotonia congenita.

Haushalter's Case Three had a less favourable outcome. As an infant, this girl did not move her arms or legs, and was never able to sit up alone. At the age of 8 months she could move her legs weakly and her arms were then noticeably weak. By the age of $12\frac{1}{2}$ years there was severe kyphoscoliosis, and she was only able to sit up in bed with her chest lying against her abdomen. There was diffuse muscular wasting and no movement could be made with the legs. She died at the age of $13\frac{1}{2}$ years. On postmortem examination the spinal cord and nerve roots were found to be normal, as were also the peripheral nerves. The atrophied muscles contained fibres of all sizes, large, medium and small. Connective tissue hyperplasia both surrounded the fascicles and invaded them, breaking them up into smaller groups of fibres. The dorsolumbar and arm muscles consisted of scleroadipose tissue in which small muscle fibres were seen; in the calves muscle fibres lay, isolated or in thin bundles, in fibroadipose tissue. The absence of lesions in the spinal cord and nerves in this case, along with a severe degree of muscular atrophy and fibrosis, suggests a primary disease of muscle which, from its course, appears to have been a congenital muscular dystrophy.

The family reported by Turner (1940, 1949) also appears to fall in this

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group. Of thirteen children, six were extremely hypotonic at birth, and probably before this as they had noticeably weak fœtal movements. Five of these children were examined at the National Hospital, Queen Square, at ages varying from 14 months to 4 years, by Batten and Risien Russell. Batten considered them to be cases of congenital muscular dystrophy. Two died in childhood; the other four improved and became able to walk between the ages of $4\frac{1}{2}$ and $5\frac{1}{2}$ years. Localized wasting was noted in the sterno-cleido-mastoids in one child at the age of 6, and in the others between 11 and 13 years. When examined by Turner, at the ages of 29, 27, 25, and 18 years, there was localized wasting of the sterno-cleido-mastoids, pectorals, trapezii and triceps, and to a less degree in the serratus magnus, spinati, latissimus dorsi and deltoids. There was also weakness of the quadriceps femoris and hip muscles, so that three of the patients walked with a waddling gait and some lordosis. But they were active and the three eldest were able to earn their living. The youngster suffered from rheumatic heart disease which led to her death. In the post-mortem examination of this case, which was made by one of us (J. G. G.) no loss of ventral horn cells, atrophy of nerve roots or other change in the central nervous system was found. Of the many muscles examined the more affected showed changes which were interpreted as those of muscular dystrophy. Most of the muscle fibres were small, between 20 and 30 $\mu$ in diameter, but a few larger fibres up to 50 $\mu$ were found. Chains of internal nuclei were not uncommon, and many small groups of sarcolemmal nuclei were also present. Cloudy changes and invasion by histiocytes were seen in isolated fibres.

Other cases with pathological examinations which could be interpreted as showing evidence of muscular dystrophy were reported by Brandt (1950) and by Richter and Humphreys (1955). Brandt's 3 cases, selected from 131 personal cases of congenital or early infantile hypotonia, were aged 4 weeks, $2\frac{1}{4}$ years, and $2\frac{3}{4}$ years, at the time of muscle biopsy. The first of these is rather too young for definite diagnosis and of the other two, the author says that "it is hardly possible to be absolutely certain of the diagnosis of myopathy." The case reported by Dubois, Graffar, and Ley (1946–1947, also Ley 1954) seems more doubtful.

Banker, Victor and Adams (1957) have also classed as dystrophic the cases reported by Spiller (1904-5), Collier and Holmes (1909), Lereboullet and Baudouin (1909), Councilman and Dunn (1911), and de Lange (1937). In our view the histology of the muscles, as reported in these cases, does not justify this diagnosis. In Spiller's case, as has been seen, the muscle fibres were normal, although of small size, and in the other 4 cases, the histological appearances were those of the Werdnig-Hoffmann disease. Collier and Holmes (1909) found loss of ventral horn cells and slenderness and loss of myelin in ventral roots in their case, and although, in the other 3 cases, no definite changes were seen in the spinal cord,

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this does not, in our view, exclude the diagnosis of Werdnig-Hoffmann disease in its earlier stages. This question will be discussed later.

There are, therefore, very few cases in the literature in which the diagnosis of congenital muscular dystrophy has received pathological confirmation, but in a few this diagnosis seems to be well established. The relationship of muscular dystrophy to congenital contractures of muscle, in cases with the clinical picture of arthrogryposis, will be discussed later.

Post-mortem examinations of cases corresponding to Oppenheim's conception of amyotonia congenita are naturally extremely rare, and with the exception of Spiller's doubtful case, we know of no such report. Muscle biopsies showing entirely normal appearances have, however, been made by Brandt (1950) and Walton (1957). Brandt accepted 10 of his 156 cases as agreeing with this diagnosis. Walton, in a series of 109 cases diagnosed as amyotonia congenita, mostly in London hospitals, found 8 cases with complete, and 9 with incomplete, recovery, and muscle biopsies in 6 of these cases showed normal appearances. Several of his cases with incomplete recovery resembled the Batten-Turner family (1940–1949), and might be more correctly diagnosed as muscular dystrophy. Weakness was most marked in the sterno-cleido-mastoids and in the proximal limb muscles; some walked with a waddle, or had difficulty in climbing stairs. In 1 case, a second cousin had muscular dystrophy. Reference has already been made to the familial case reported by Silvestri (1909), in which the clinical evidence for muscular dystrophy was strong.

Recent studies have shown two further possible types of change in the muscles of children with the syndrome of congenital or early infantile hypotonia.

(4) *Central core disease.*—Shy and Magee (1956) described 5 cases, in three generations of a family, in which limpness and weakness had been present from birth, or had been noticed shortly thereafter. The grandfather and his affected son and daughter first began to walk during their 5th year. One of the two affected grandsons walked at the normal age of 14 months, but was still, at the age of 4 years, unable to run and to climb onto a chair like normal children. In the other affected grandson, walking was delayed until the age of 20 months, and at $2\frac{1}{2}$ years he walked with a waddling gait and showed weakness in movements of the shoulders and hips. The three older patients were still weak in the hip muscles, and those in the second generation also in the sterno-cleido-mastoid and shoulder girdle muscles, but this weakness had not increased.

Biopsies in all 5 cases showed similar appearances. The muscle fibres were larger than normal; the majority measured approximately 80 $\mu$, and some large fibres reached 240 $\mu$ in diameter. In almost every fibre there was a central core of more closely set myofibrils which appeared more amorphous than the surrounding zone. These myofibrils stained blue, instead of the normal purple, with Gomori's trichrome stain (fig. 9);

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in hæmatoxylin eosin preparations they were rather more eosinophilic and they stained rather more strongly than the outer zone of myofibrils by the PAS method. We shall refer to this curious myopathy as "central core disease."

(5) *Polymyositis.*—Walton (1956*a* and *b*) and Walton and Adams (1958) consider that polymyositis occurring in early infancy may produce a clinical picture resembling Oppenheim's disease, or congenital muscular dystrophy. These authors describe a case in which weakness was present soon after birth; in spite of some progress of the disease, the child was alive at 8 years of age when biopsy was performed. This showed areas of degeneration and necrosis of muscle fibres and small celled infiltration with a striking increase in fibrous tissue. They refer to a similar case recorded by Bovet (1936).

There appear, from the literature, to be at least five different conditions of muscle which can produce the clinical syndrome of weakness and hypotonia at birth or in the early weeks of life. These are (1) Spinal infantile muscular atrophy; (2) True amyotonia congenita (Oppenheim), or "benign congenital hypotonia" (Walton); (3) Congenital or early infantile muscular dystrophy of Batten; (4) Central core disease of Shy and Magee; (5) Polymyositis. This list does not include the many general diseases, such as rickets, or the hypotonic forms of cerebral diplegia, or mental deficiency, among which mongoloid idiocy is a well-recognized form. In these general or cerebral diseases the muscle may be expected to have a normal microscopical appearance, although in some forms, especially those associated with considerable inertia, the fibres may be smaller than normal.

## Present Material

If these five conditions of congenital or early infantile muscular hypotonia can be distinguished by muscle biopsy, we should be able to make a more exact diagnosis and prognosis than is otherwise possible, and, if the disease is polymyositis, to institute treatment which may be beneficial. It is the object of this paper to examine these possibilities in the light of muscle biopsies in cases of infantile hypotonia. The present series of "Floppy infants" numbers 23 (Table I). Of these, 11 were compatible with infantile spinal atrophy. 3 such cases are described. 2 of these were followed for $2\frac{1}{2}$ years. 1 of these 2 warranted separate description, in that she is at the present time 31 years of age. The third patient is described in detail in that this patient was the youngest (28 days) biopsied (fig. 1). The remaining 12 patients consisted of 3 with progressive myopathy, 2 with benign congenital hypotonia, 5 with central core disease (previously reported and hence not recorded in detail here), and 2 with congenital sporadic progressive myopathy with joint deformities (arthrogryposis multiplex congenita).



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The 3 examples of infantile spinal atrophy are as follows:

L. P., a white female, was admitted for the first time in 1955, at the age of 28 years. Her history was one of progressive weakness, beginning in early infancy, and involving neck, trunk, all extremities, and more recently, muscles of mastication. She was an only child. During gestation, her mother gained about 100 lb. Delivery was by forceps. Weight at birth was 9 lb. The infant seemed normal. She moved her extremities adequately during the first week. It is believed that weakness of the lower extremities began at 10 days. Perhaps normal movement of her neck persisted during the first few months of life. She did not sit properly without support; weakness of the trunk interfered with balance. She did not learn to walk. As a youngster in a stroller, she was able to push slightly with her legs, thus propelling the stroller backwards. During her early years, she was able to extend her right leg. She used this leg and both upper extremities to slide slowly down the stairs.

Although weakness was marked in the trunk and lower extremities from early infancy, the function in her hands was thought to be normal for the first few years following birth. She recalled that her joints were pliable and she could easily place her feet behind her neck; her hands and wrists were hyper-extensible. Weakness of the arms began at the age of 3 or 4 years, and progressed. Severe weakness began in infancy, progressed slowly for many years, and then progressed a little more rapidly since the age of 20. This included all extremities, and was greater proximally than distally. At the age of 25, there was weakness of the jaw, and difficulty chewing and swallowing. The tongue felt tired more easily. Spontaneous twitchings were reported in the left arm and lower face.

The only abnormality of sensation was a small area of numbness on the back of the left arm, which persisted unchanged for at least six years preceding this admission. Review of systems revealed "extrasystoles" following meals and during the night for the past few years. Past health was good, except for her severe neurological disease. Family history was essentially negative for neurological or muscular disease.

*Examination.*—General physical examination in 1955 showed a well-nourished, alert young woman with pronounced scoliosis of the dorsal lumbar spine and distortion of the thoracic cage. There was mottling of the skin of the lower extremities. The remainder of the physical examination was essentially negative.

Neurologic examination revealed a severely disabled woman. When lying in bed, she was unable to care for herself. When placed in the sitting position, she was able to hold her head erect. There were some useful functions in the distal parts of the upper extremities. Because of subcutaneous tissue, wasting was not apparent except in the forearms and intrinsic muscles of the hands. The muscles innervated by the fifth, eleventh, and twelfth cranial nerves were involved. There was weakness of muscles of the jaw, involving the left side more than the right. Sterno-cleido-mastoids and trapezius muscles were weak. The tongue showed some atrophy. The shoulder girdle was severely involved. A flicker of contraction was palpated in the triceps bilaterally. Both arms could be elevated above the shoulder level. The biceps and distal musculature functioned against gravity, and with slight resistance. The intercostals and pectorals did not appear to function at all. Breathing was diaphragmatic and abdominal. Lower extremities were more involved than the upper. There was a flicker of contraction in the right quadriceps, and slight internal rotation. There was a little function below the knees. Moderate plantar flexion and dorsiflexion of the ankles, extension and flexion of the toes, were present. Deep tendon reflexes were not elicited. The only sensory abnormality was a small area, 5 cm. in diameter, on the posterior lateral aspect of left arm (axillary nerve), with decreased sensitivity to touch and pin-prick.

Routine laboratory studies were within normal limits. Electrocardiogram showed

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left axis deviation and ventricular premature contractions. The diaphragm moved normally under fluoroscopy. X-ray showed marked scoliosis of the dorsal lumbar spine. Skull showed unusual thickness of the parietal and frontal bones, otherwise negative.

Biopsy of the right biceps brachii showed a large group of small fibres up to 20 micra in diameter, in both cross and longitudinal sections. There was an apparent increase of external nuclei in these fields. Cross striations were well preserved. Other fibres of medium size, or larger fibres (up to 120 micra) showed internal nuclei, but no structural changes. Collagen and fat were not increased.

*Readmission.*—The patient was admitted for further study in 1958 at the age of 31 years. There was an increase in weakness of the upper extremities, including loss of function of the right deltoid. She could no longer elevate this arm above her head. A flicker of contraction was palpable. When chewing and swallowing food, she tired more easily. Her voice was slightly hoarse. Extrasystoles occurred more frequently. She had no febrile illness or respiratory infection during this interval.

General physical examination was essentially unchanged. Respiration was almost entirely diaphragmatic. Neurologic examination revealed occasional fasciculations of the dorsal interossei of both hands and the left lower face. The tongue showed marked wasting and fasciculations. There was an increase in weakness of the right deltoid, as stated above. There was slight increase in weakness of the rest of the upper extremities. Other muscle groups were essentially the same. Contraction of the recti abdominis was weak, and asymmetrical, being a little stronger on the right. A slight contraction of the right quadriceps was still present. Deep tendon reflexes were barely elicited in both lower extremities (patellar and Achilles) and equal bilaterally. The right abdominal reflexes were elicited; the left absent. Plantar stimulation produced no movement of the toes in either direction. Sensory examination showed persistence of the small area of "numbness" on the left arm. However, pin-prick was reported dull, but light touch and temperature were essentially normal. Otherwise, sensation was completely intact.

Routine laboratory studies were within normal limits. Electrocardiogram was unchanged. Galvanic and faradic stimulation of the right deltoid and right quadriceps evoked no response; a rheobase could not be found.

A biopsy of the right deltoid revealed a severe loss of muscle fibres and a large amount of fat and collagen. There were insufficient fibres remaining to allow a diagnosis, but these remaining were in small groups and showed no structural change within fibres or nuclei.

An electromyogram was performed using a monopolar needle electrode. The left biceps brachii showed electrical silence at rest, and adequate action potentials on contraction. Fibrillations were found in the first dorsal interosseous, and right biceps brachii, and fasciculations in the abductor digiti quinti. Low, but adequate, action potentials were present. Spontaneous waves of 40 microvolts, 3 milliseconds and less, occurring irregularly at thirty per second were "fibrillations." Spontaneous waves of 500 microvolts, most, deeply notched near the top, 6 milliseconds in duration were "fasciculations." All action potentials showed varying

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frequency interference. They were polyphasic averaging 700 to 1,000 microvolts in amplitude and 4 to 10 milliseconds in duration.

*Diagnosis.*—Progressive spinal and bulbar muscular atrophy, neurogenic type, beginning in infancy, Werdnig-Hoffmann's disease.

D. D., a 2½-year-old white female, was admitted in 1955, with a history of progressive weakness and loss of motor function. She was the product of a normal full-term pregnancy. The child was a healthy, apparently normal youngster during the first few months of life. At 9 months of age, she was unable to sit alone, and unable to hold her head up when lifted in the supine position. Her course was slowly downhill, losing previous attainments. She lost the ability to move and lift her legs some time after 8 months. She was unable to sit without support and unable to stand. General health was good. Family history was essentially negative for neurological or muscular diseases. Two older siblings were normal, healthy youngsters.

Examination in 1955 showed a small, thin child, weighing ten kilograms. General physical examination was within normal limits. Neurological examination showed involvement of muscles supplied by the fifth and eleventh cranial nerves and motor involvement of all extremities, trunk and neck. Diminished strength of jaws in chewing and biting was present bilaterally. There was weakness on extension and flexion of the neck. Weakness of trunk was accompanied by a deformity of the thoracic cage, and reduced expansion of the chest during respiration. Weakness of the extremities was greater proximally than distally, and greater in the lower than in the upper extremities. The patient could still elevate her arms above the shoulder level against gravity, but not against resistance. She used her hands well. There was almost complete flaccidity of both lower extremities, and almost complete absence of voluntary activity. The child was unable to sit without support and unable to roll over. Fasciculations were not present. Deep tendon reflexes were not elicited. Sensation to pin-prick was intact.

Routine laboratory studies, including electrocardiogram and X-rays of chest and skull were within normal limits.

Biopsy of vastus lateralis was performed; there was considerable subcutaneous fat and small muscle mass. Histologic examination showed large groups, even whole fascicles of small muscle fibres, 5 to 15 micra in diameter (fig. 4). Remaining fibres varied from 20 to 60 micra in diameter, and showed no alteration of structure (fig. 5). Lymphocytes were present around a blood vessel. Some of the peripheral nerves showed fibrosis of endoneurium. In summary, this was compatible with neurogenic type of muscular atrophy with endoneural fibrosis.

The patient was re-examined in 1958, at 5 years of age, and showed marked wasting and weakness. One month before admission, she had a respiratory infection with fever, cough and pain in the chest. General physical examination showed a thin, pale child with marked scoliosis of the dorsolumbar spine. Heart and lungs were essentially negative. The twelfth cranial nerve was involved at this time; the tongue showed some atrophy and a few fine movements, believed to be fibrillations. The pattern of weakness was essentially the same, but increased. There was slight inco-ordination of the upper extremities, due to weakness. Deep tendon reflexes were absent. Flexion of the toes followed plantar stimulation. Sensation was intact, including vibratory and position sense, light touch, and pain sensation. In breathing, the diaphragm and the pectoral muscles moved synchronously.

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An electromyogram was performed. A monopolar needle electrode was inserted into the quadriceps muscle. There was some activity during "rest," but definitely not fibrillation and not fasciculations. There were a few small waves of long duration following contraction, and were interpreted as a lack of relaxation. These waves measured 50 to 100 microvolts and lasted 6 to 8 milliseconds. On contraction polyphasic waves, of varying amplitude not higher than 400 microvolts and 8 to 16 milliseconds, were present. X-rays of all extremities showed long, thin bones and diminished muscle mass in relation to soft tissues (fig. 2).

*Diagnosis.*—Infantile spinal and bulbar muscular atrophy, neurogenic type; Werdnig-Hoffmann's disease.

P. S., a 23-day-old white female infant, was admitted in 1958, with a history of hypotonia since birth. The child was quite floppy. Pregnancy was full term and uneventful, with presumably adequate fœtal movements until the last week, when the child seemed less active. The labour lasted four hours. The delivery was by low forceps; amniotic fluid was meconium stained. Fœtal heart sounds were reported "normal." Lethargy and lack of spontaneous activity were recognized during the first twenty-four hours. This hypotonic state persisted.

Laboratory studies from another hospital reported the mother to be Rh negative. The Rh titre during the sixth month of gestation was negative. X-rays, spinal fluid, urinalysis, serum creatinine were within normal limits.

There was no known family history of neurologic or muscular disease.

At the time of admission the child weighed 8 lb. and showed little spontaneous movement other than breathing, which was rapid and abdominal. Her cry was feeble. She sucked the bottle well. The head was a little elongated. The anterior fontanel measured 10 by 12 mm. The posterior fontanel measured 3 mm. There were two mid-line capillary hæmangiomata over the occipital area. The remainder of the general physical examination was within normal limits. Joints were not hyperextensible.

Neurologic examination showed marked involvement of the motor system. Wasting was not apparent. There was marked hypotonia of all extremities, neck and trunk. There was marked weakness, except for the face. There was slight movement of the hands; the rest of the extremities did not move. Deep tendon reflexes were not elicited. Prostigmine 0·125 mg. did not improve strength.

Routine laboratory studies were non-contributory. Protein bound iodine was 7·1 mg. Cholesterol was 137 mg.

A biopsy of the vastus lateralis at the age of 28 days showed uniformly small fibres throughout, except one area near the periphery, composed of a small group of relatively large fibres, with no structural changes. Of the small fibres most were 5 to 10 micra, but some were less than 5, and the largest 17 micra. A few small fibres had prominent granules, but no other structural changes. Internal nuclei were not present. The field showed a relative increase in external nuclei. Endomysial fat and connective tissue were not increased. The essential findings were (1) uniformly small fibres predominating, (2) the absence of Wohlfart's B fibres, and (3) the presence of a small group of larger fibres near the periphery.

A biopsy of the vastus lateralis was performed at the age of 49 days and showed many large groups of small fibres, 5 to 10 micra. In other

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bundles occasional fibres reached a diameter of 20 to 30 micra. There were too many of these to be simply B-fibres. Perivascular lymphocytic infiltration was prominent. Endomysial connective tissue was not increased. Perimysial connective tissue was increased.

Electromyogram was performed using a monopolar needle electrode. The quadriceps showed electrical silence at rest, and no evidence of action potentials. The gastrocnemius showed some background activity, which probably represented low action potentials, for these increased with crying and tenseness. Fibrillations and fasciculations were not present. The biceps brachii was similar to that of the gastrocnemius. Potentials were of varying amplitude and frequency, mostly 100 to 150 microvolts and 8 to 12 milliseconds.

*Diagnosis.*—Infantile spinal muscular atrophy, neurogenic type; Werdnig-Hoffmann's disease.

3 patients had pathology compatible with a progressive myopathy. 2 were familial and 1, D. W., sporadic.

D. W. was admitted in October 1955, at the age of 3 years and 10 months. The mother's pregnancy was uneventful and full term. Fœtal movements were considered normal, and about the same as the fœtal movements in a previous and subsequent pregnancy. The child was considered normal at birth. During the first six months the child was irritable. At the age of 6 months, he received iron for anæmia. When 7 months old, the child sat without support. He did not learn to crawl, but learned to pull himself across the floor with his upper extremities and trunk. He was able to stand and to walk at 16 months of age. However, walking was accompanied by frequent falls. Running was slow and awkward. Climbing stairs was slow and difficult. General health was good, although the child had frequent, but mild, colds during the winter. At a younger age the child had prostigmine daily for one month, and alpha-tocopherol acetate for several months, neither of which improved the clinical picture. The family history reveals a maternal uncle, age 33 years, who has "cerebral palsy." There is no further history of neurologic or muscular disease in the family. Two sisters, ages 1 year and 5 years, are reported in good health.

*Examination.*—The child was slender and of average height and weight. Abnormalities were limited to the motor system. Although muscle wasting was not definite, the relatively large calves with slender extremities suggested decrease in muscle mass of the thighs. The calves were not considered larger than "normal." He was able to use his upper extremities well. He walked with a slight waddle. Running was slow and awkward. He was able to climb stairs slowly, and when rising from the floor, or a low seat, he required the use of his hands to push against his lower extremities. The greatest weakness was in the proximal muscles of the extremities. Deep tendon reflexes were absent in the upper extremities. Patellar reflexes were slight, but equal bilaterally. Achilles reflexes were absent. Pathological cutaneous reflexes were not present. Sensation to pin-prick was intact. Cranial nerves were normal.

*Laboratory.*—Routine studies were essentially normal.

*Biopsy.*—The specimen was obtained from the vastus lateralis. It showed severely involved muscle, in which the pattern of the lesion was one of changes in isolated muscle fibres. The size of fibres ranged from 5 to 110 micra in diameter. Loss of cross striations was present

in both small and medium sized fibres. Some of the fibres were cloudy, and some showed floccular changes. Phagocytes were present, within and adjacent to floccular fibres. Groups of small basophilic fibres with prominent and vesicular fibres were interpreted as "regeneration" (figs. 6 and 7). Internal and external nuclei were increased. The conclusion was severe myopathy with marked structural and phagocytic changes, and with a tendency to regeneration.

*Readmission.*—The patient was admitted for the second time in February 1958, at the age of 6 years. His mother stated that since his previous discharge he was no worse, and in some ways seemed better. He did not fall as frequently while walking. Examination revealed a thin, pale child of average size. Both calves appeared prominent with increased local heat on palpation. The thorax showed slight asymmetry, the left anterior part appearing a little flat in comparison to the right. Breathing utilized intercostal muscles as well as the diaphragm. Posteriorly, there was winging and "looseness" of both scapulæ. In the lower extremities there was slight subluxation of the fourth and fifth metatarsals. Motor performance was unchanged. Muscle weakness involved the neck (sterno-cleido-mastoids), trunk and all extremities. It was symmetrical and mainly proximal. In the lower extremities there was distal weakness also, with weakness of the tibialis anticus. All muscles graded III and IV (Medical Research Council). At this age the child was able to co-operate better for a manual muscle test than on the previous admission, therefore, in view of continued level of performance, it is probable that the amount of weakness of individual muscles apparent at this time may have been present two and a half years ago. Muscle tone was essentially normal. There were no fasciculations. Except for running, co-ordination was good. The only deep tendon reflexes elicited were the patellar reflexes, which were of average activity and equal bilaterally. Abdominal reflexes were present. Plantar response was one of flexion. Sensation was normal. Mental state was appropriate for his age.

*Electromyography.*—The gastrocnemius muscle was examined using a monopolar needle electrode. Initially, there was silence at rest. Following tapping there was a series of rapid, low waves accompanied by a low pitched rumble, suggestive of myotonia. These waves were monophasic, thirty microvolts in amplitude, four milliseconds long, occurring irregularly about one hundred per second. At another time, a few rapid waves of shorter duration followed tapping. These resembled fibrillation. On contraction, action potentials were polyphasic of low amplitude, 300 microvolts, lasting 8 to 12 milliseconds.

*Diagnosis.*—Myopathy, of early onset or congenital.

Of the two siblings with progressive myopathy, but one is illustrated. If the older sibling had not been examined, this patient could have been called arthrogryposis multiplex. The older sibling (Table I see over) did not have joint deformities.

J. M. was admitted in November 1957, at the age of 2½ years. The child was the product of a full-term pregnancy and spontaneous delivery, without anæsthesia. The mother reported few fœtal movements. At birth he weighed 6 lb. 8 oz. He was thought to be "flaccid"; both feet were plantar flexed, and could not be corrected. He was never able to lift his hand up from a prone or supine position. He sat supported with

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pillows at 12 months, and alone at 15 months. He has never been able to roll over, to place himself into a sitting position, to crawl or to stand. Mentally, he was considered normal and began to speak at a year and a half. General health was good. A review of the family history reveals a similar disease, in onset, course, and findings in a four-year-old sister. There was no other neurologic or muscular disease involving other members of the family. The disease was present at birth; there is no history of gain in motor power, followed by regression.

*Examination.*—The child was small and slender with a relatively large head, 48 cm. in circumference. Chest measured 43 cm. in circumference. When placed in a sitting position, he was able to maintain his head erect, but when his head was flexed or extended, he was unable to bring it to a neutral position. Although respiratory movements were not vigorous, there was a symmetrical expansion of the chest and excursion of the diaphragm. In the examination of the cranial nerves it was noted that there was paucity of facial movement on conversation and attempts at smiling. Closure of the eyelids was weak. The remainder of the examination of cranial nerves was normal. Wasting was evident in the trunk and all extremities. Wasting and weakness was symmetrical and greater proximally than distally in the upper extremities. There was winging of both scapulæ. He could not elevate his arms against gravity. Flexion and extension of the forearm were barely accomplished against gravity. Grasp was weak, although some of the movements of his fingers were accomplished against resistance. Pronounced weakness was present throughout. Both lower extremities had equinovarus deformities of the feet. Deep tendon reflexes were absent throughout. Plantar stimulation elicited slight curling of the toes. Sensory examination reveals no impairment of light touch and pain. Fasciculations were not present.

*Laboratory.*—Routine studies were non-contributory. X-rays showed decreased muscle bulk about the shoulder.

*Biopsy.*—Examination of a specimen from the vastus lateralis showed a widespread lesion. There was significant variation in size of individual muscle fibres, ranging from 5 to 50 micra in diameter. Structural changes included granular and floccular changes. External nuclei were oval or elongated, and many contained prominent nucleoli. There were collections of round cells, compatible with inflammatory changes (fig. 8). Endomysial fat and collagen were increased markedly (fig. 3). Blood vessels were normal. In conclusion, the impression was severe myopathy. (Note: This was similar to biopsy study of his 4-year-old sister.)

*Electromyography.*—The left gastrocnemius was examined using a monopolar needle electrode. At rest, there was electrical silence. With effort, low action potentials 100 to 150 microvolts were present. Potentials were rapid and of varying amplitude.

*Diagnosis.*—Congenital myopathy, also present in a sibling. (Note: The biopsy of his sister, S. M., showed a wide variation in size of fibre, from less than 10 micra to 70 micra. A few internal nuclei were present. An area of large basophilic fibres with vesicular nuclei, compatible with regeneration was present. A large amount of endomysial collagen and fat was present (fig. 10). However, structural changes within the fibre were observed only in J. M.)

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An example of benign congenital myotonia is as follows:

S. L. was admitted in 1955 at the age of 2 years. The mother's pregnancy was full term and normal, but fœtal movements were less with this pregnancy than with the mother's two previous ones. Delivery was normal. At birth the child appeared normal and weighed 7 lb. 2 oz. On the third day the child was examined because of fever, and at that time it was noted that muscle tone was decreased considerably. The child was too weak to suck and for the first four months, was fed with a small rubber tube attached to an asepto syringe. At 4 months she was able to suck from a soft nipple. She held her head up at 5 or 6 months. If placed in a sitting position, she was able to remain sitting without support at 1 year of age. At 18 months she began to roll over in order to move. At 2 years she was able to sit upright and scoot on her buttocks, pushing with her heels. The child used her upper extremities fairly well, and was able to feed herself at 13 months of age. Past health was very good. Family history was negative for neurologic or muscular disease.

*Examination.*—The child was alert and appeared of average mentality, although unable to talk. She was able to sit alone and scoot rapidly across the floor. Physical examination was non-contributory, except for neurological findings. Cranial nerves were essentially normal. There was symmetrical weakness of all extremities, greater proximally. Wasting was not apparent. The lower extremities were much more involved than the upper extremities. She was unable to stand. Her arms were weak although her hands were quite strong. The deep tendon reflexes that were elicited were equal bilaterally; reflexes of the biceps brachii were slight, and patellar reflexes were average. Triceps and Achilles reflexes were absent. Superficial reflexes were present. There were no pathological reflexes. Sensation to pin-prick was intact.

*Laboratory.*—X-rays and routine studies were within normal limits.

*Biopsy.*—On microscopic examination the vastus lateralis revealed muscle fibres averaging 20 micra in diameter. However, some were as small as 10 micra, and as large as 40 micra (fig. 11). Wohlfart's "B fibres" were not prominent. Most of the fibres had only one nucleus in cross section. No structural changes were present. Collagen and fat were not increased. Peripheral nerves appeared normal.

*Out-patient follow-up.*—In 1956, psychological testing showed the child to be of average intelligence. She did poorly on items requiring verbalization. Physically she improved in the use of all extremities. Muscle strength increased slowly and at 2 years and 8 months, she was able to stand from a sitting position, unaided, and within a few weeks was able to walk alone. Deep tendon reflexes could be elicited in all extremities. Muscle tone, although still decreased, had improved. Speech increased in vocabulary and pronunciation became clearer.

*Readmission.*—At the age of $3\frac{1}{2}$, the patient was walking well and speech, although improved, was still inadequate in quantity. Her teeth were in poor condition with areas of softening and erosion. She had gained weight steadily and now weighed 40 lb. Her general health had been good. At this time she had a respiratory infection, not severe. Pharynx and tonsils were slightly red. Rhonchi were present, but cleared with coughing. Neurologic examination revealed normal cranial nerves. Proximal weakness was still present in all extremities, but the child walked well, although with a slight waddle, and used all extremities adequately. Because of obesity muscle bulk could not be determined. Tone was slightly decreased in all extremities and co-ordination was essentially normal. Perception of pin-prick and light touch was present throughout.

*Diagnosis.*—Slow motor development in a child of normal mentality. Benign congenital hypotonia.

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Two patients were diagnosed originally as arthrogryposis multiplex congenita. As these were similar, but one example is given below:

N. F. was admitted December 1956, at the age of 4 years, with a history of muscle weakness, recognized during infancy, and worsening during the past year. The patient was the product of a normal full-term pregnancy, born by Cæsarean section. Deformities were present at birth. The feet were dorsiflexed and everted; the hands were markedly flexed at the wrists. Correction with plaster casts was attempted, but was unsuccessful. The patient moved his arms and legs well during the first few months of life. He sat alone at 8 months. A diagnosis of "congenital muscular deficiency" was said to have been made when the child was 10 months old. However, the child continued to make gains, crawling at 1 year, arising from the supine to a sitting position at 16 months, and pulling himself to his feet by hanging on the rails of the bed at the age of 17 months. Improvement was slow until the age of 3 years. He did not learn to walk. During the past year, he lost the ability to pull himself to a standing position and to use his upper and lower extremities as well as previously. Mentally, the patient was alert and seemed normal. Past medical history included "colds" and "tonsillitis" at the age of 2 years. There was no history of neurologic or muscular disease involving other members of the family. Two siblings were reported to be in good health.

*Examination.*—The patient was a small, inactive youngster with feet everted and dorsiflexed and wrists held flexed (fig. 12), whose general physical examination, other than the above, revealed nothing of note. The only abnormalities of cranial nerves were involvement of the eleventh cranial nerve, with bilateral weakness of sterno-cleido-mastoid and trapezius muscles; and seventh cranial nerve, manifested by feebly performed facial movements. Muscle weakness otherwise was general and most marked in the extremities. In the upper extremities the weakness was greater distally, and in the lower extremities, extensive throughout. When the child sat, there was a mild dorsal kyphosis and sagging of the trunk. Muscle tone was diminished throughout. Wasting was not apparent. Fasciculations were not seen. Deep tendon reflexes were weak but present throughout. Abdominal reflexes were equal and brisk. There were no pathological reflexes. Tests of co-ordination were performed well within the limits of muscle strength. He was able to move along the floor in a sitting position propelling his body with his legs, and also turning his knees from side to side. When supine, he could sit only by rolling over into a prone position and pushing up with his arms. Sensation was normal.

*Laboratory.*—Routine laboratory studies were essentially normal. X-rays of the extremities showed bony demineralization.

*Biopsy.*—Histologic study of the vastus lateralis muscle showed a spectrum of sizes (fig. 13). The largest muscle fibre measured 130 micra. There were basophilic fibres and large clear nuclei (fig. 14), compatible with regeneration. Phagocytosis was present also. Impression: Myopathy.

*Diagnosis.*—Myopathy associated with arthrogryposis multiplex congenita.

## Discussion

A survey of microscopic preparations from hypotonic infants allows the pathologist to readily separate four major types of disease. If one adds, in addition, clinical criteria, then a fifth type may be subdivided from these four. In the early stages of the disease, a clinical separation may be indeed difficult. The prognosis, however, rests upon such a

separation. In our experience the muscle biopsy becomes invaluable in the final solution.

If the process becomes evident after a period of what may be considered nearly normal infancy, or if bulbar muscles are involved, or if there is wasting or involuntary fascicular movement in the tongue then one may justifiably consider infantile spinal (and bulbar) atrophy the most likely diagnosis. In most series of hypotonic infants with normal mentation this disease accounts for the majority.

The microscopic picture in the presence or absence of the above findings is almost pathognomonic. Large groups of small fibres may be seen on cross section with occasional sparing of normal or perhaps slightly hypertrophied fibres (fig. 15), giving the characteristic pattern of neuropathy (Wohlfart, 1949). Equally characteristic in this disease is the lack of endomysial collagen proliferation. There may be excessive epimysial or perimysial collagen, but this may also occur in the normal (Greenfield *et al.*, 1957). The architecture of the involved atrophic fibres was unaffected until the size reduction reached 5μ or less. There may or may not be small focal collections of lymphocytes about intramuscular blood vessels, but these should not be considered evidence of inflammation in the absence of inflammation elsewhere. The youngest patient biopsied in this series was 28 days. In the biopsy so obtained only 4–5 large fibres were recorded in a "sea" of small fibres. A repeat biopsy twenty-one days later showed the typical groups of small fibres interspersed with larger fibres. While this may be a reflection of the random nature of the biopsy, an alternative could be that the unaffected fibres must reach a size in which they may be differentiated from the atrophic fibres. If the latter is the case then biopsy should be deferred until at least the second postnatal month. The oldest recorded patient in this series of infantile spinal atrophy was 31. This was clearly a case of a progressive affliction of spinal and bulbar musculature, dating from the first months of life. During the two and a half years this patient was observed by us, marked weakness and atrophy of the deltoid and lingual muscles occurred. Thus, in the very rare case, slow progression is possible. In older age groups (i.e. 5 and over) fasciculatory movements in wasting muscle becomes prominent. Patients so involved obviously summate algebraically with their normal growth. Thus, if the process is rapid, they will (as in the majority) become steadily incapacitated. If the process slows, they may show periods of remission, or may even appear for a time to improve. Thus, the muscle biopsy becomes all-important as to the final outcome. The presence of cases reported with normal anterior horn cells, but characteristic muscle pathology, raises the intriguing possibility of abnormal end-plates (Coërs and Pelc, 1954).

The group encountered next most frequently in this study was the flaccid infant from the time of birth, who obviously improved with the

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passage of time. Here again proximal muscles were more selectively involved than distal musculature. In the early stages difficulty in sucking and swallowing were recorded, as well as diminished or absent reflexes. Psychological testing of these children, later in the course of the disease, showed universal impairment. Unfortunately such testing at this age depends largely on performance testing. Some of these children now have been followed for four or more years and are demonstrating normal intelligence. For the purpose of this communication, only 2 cases are recorded as these are the only 2 which at this time have been followed long enough to show normal intelligence. This accentuates the difficulty of rejecting mental deficiency as a cause of hypotonia.

Both of these cases demonstrated no structural change of the muscle fibres on microscopic examination. One showed universally small fibres (Spiller, 1905) without group lesions. Both were rebiopsied two and a half years after the first biopsy, with a similar picture seen both times. No connective tissue, or cellular abnormality was to be seen. The muscle spindles and intramuscular nerves were within normal limits.

These cases would correspond, then, to those described clinically by Oppenheim (1900), pathologically by Spiller (1904-5), and Walton (1956*b*), and we would agree with the latter that the term "benign congenital hypotonia" should be used for this group. This is particularly true in that Oppenheim probably had a mixture of disorders in his "Myatonia Congenita." Since all such cases apparently improve (Walton, 1956–1957; Haushalter, 1920), the muscle biopsy again is of importance.

The entity of "central core" disease has been recently described (Shy and Magee, 1956) as another cause of hypotonia in infancy. This disease again involved proximal muscles, but is distinguished by the preservation of reflexes, non-progression, but also no improvement, sparing of bulbar musculature, and a characteristic pathognomonic finding in the biopsied specimen of central areas of basophilic fibres, which are packed closer together and which contract independently of the peripheral fibrils (fig. 3).

This leaves, then, the one entity of an infantile myopathy, of which there are five in this series. If one rejects these patients with joint deformities as "arthrogryposis multiplex," then 2 of these cases of sporadic incidence would be excluded. However, of the remaining 3, 1 of 2 siblings presenting with proximal weakness also had joint deformity at birth, while the other sibling did not. Both had a pathologic picture of myopathy, as did the final patient who had no familial history, but the characteristic picture of a myopathy.

Microscopic examination of muscle biopsied in these patients presented no group lesions. Huge fibres were found, particularly in the arthrogrypotic group, measuring 150 μ, or more, in a child of but 3 years. Architectural changes in both medium and large fibres were common with phagocytosis.

Inflammation was common and extreme in the youngest of the 2 siblings (fig. 8). Perivascular polymorphonuclear cells and round cells were to be found diffusely, next to damaged fibres and within damaged fibres. In all 5 cases basophilic fibres with large vesicular nuclei and prominent nucleoli were to be found either singly or in schools (fig. 7), which we interpret as regeneration. Large quantities of endomysial collagen (fig. 10), or fat, were also found. It is of interest that this picture would correspond to Case 3 of Walton and Adams monograph (1958), and yet was to be seen in 2 siblings. This raises again the controversial point of familial myositis or acute dystrophy with marked inflammation and connective tissue response.

Whether the term "arthrogryposis" should be used for such infants who, in addition to muscular weakness and wasting, also have joint deformities, becomes a difficult decision (Middleton, 1934). Both cases reported here were myopathic and could not be distinguished from any other progressive myopathy. However, a neuropathy has been described (Adams, *et al.*, 1953), with this clinical entity. It would appear, therefore, that nothing is gained in retention of this term, and the primary pathology reported, unless clinical studies show the ultimate progress of the disease to be different.

Electromyography was performed in 9 of the patients with progressive muscular atrophy of the spinal and bulbar spinal type (Werdnig-Hoffmann's disease). A monopolar needle electrode was used to examine from one to four muscles in each patient. Only 2 showed spontaneous activity during rest. As described in the case history of L. P., a 31-year-old female, fibrillations and fasciculations were present. One youngster of 2 years, C. F., showed resting activity continuously. Monophasic and diphasic waves, 200 to 300 microvolts in amplitude, 8 to 10 milliseconds in duration, recurred at a rapid rate; there were fasciculations. Action potentials in such patients ranged from 50 microvolts to 1,000 microvolts. However, most were low, below 500 microvolts. Most were also polyphasic waves of 8 to 12 milliseconds, but the duration of some was as low as 4, and as high as 18 milliseconds. There were no series of single oscillations without interference from neighbouring fibres. Even with low action potentials, there was interference from neighbouring fibres. One patient, C. F., with spontaneous activity at rest, showed regularly recurring spikes against a background of waves of changing amplitude and frequency during contraction. This was interpreted as a combination of mixed single potentials and interference from neighbouring fibres.

In 4 patients with myopathy, one S. M., showed spontaneous activity at rest. A group of monophasic waves, 80 microvolts in amplitude, less than 2 milliseconds in duration, recurred irregularly at the rate of eight per second; these, we interpreted as fibrillations. Another patient, D. W.,

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had electrical silence at rest, but following tapping a small series of small rapid waves of low amplitude persisted several seconds, and faded away. These waves were 30 microvolts and 4 milliseconds, with a frequency of over a hundred per second. This was interpreted as the muscle component of myotonia. All 4 of these children with myopathy showed low action potentials; the highest measured 300 microvolts; most were below 150 microvolts. Many were 8 to 12 milliseconds in duration and polyphasic. All showed "interference" (Buchthal and Clemmesen, 1941). In these 13 patients the electromyogram, although interesting, proved of much less value than the muscle biopsy, both in diagnosis and prognosis. Even the finding of low action potentials in these patients need not mean pathology, for low action potentials may result in normal muscle due to lack of sufficient voluntary effort, and in a young child, whether or not effort is maximal can only be assumed. In this small series, fibrillations were present in one "neuropathy" and in one "myopathy." Although fibrillations are uncommon in myopathy, its occurrence has been reported by others (Eaton and Lambert, 1957; Norris and Chatfield, 1955; Walton, 1958). Spontaneous activity in muscle fibres cannot be a point of absolute value in diagnosis of disease.

One could conclude that Werdnig and Hoffmann, Oppenheim, and Batten were then all correct in their contentions in that there is a progressive neuropathy and a progressive myopathy—both of which may be familial; that there is a "benign congenital hypotonia" that improves, and finally there may be recognized the relative stationary type of "central core" disease.

## Summary

(1) Muscle biopsy is imperative in the understanding and ultimate prognosis of the floppy child. The prognosis may be divided into three groups: (*a*) Progressive—Infantile spinal atrophy (Werdnig-Hoffmann). Infantile progressive myopathy; (*b*) Stationary—"Central core" disease; (*c*) Improvement—"Benign congenital hypotonia" (Walton).

(2) The electromyogram is of little use in differentiation of these groups.

(3) The characteristic pathology of each is described.

(4) More information is needed as to the clinical outcome of "arthrogryposis multiplex" to warrant its separation as an independent entity.

The authors wish to acknowledge their gratitude to Mr. Charles Baker who prepared the majority of these sections, and Mr. Fred Meiller, who is responsible for the photomicrographs.

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## PLATE LIX

FIG. 1.—Patient P. S., the 23rd post-natal day. Note the extreme flaccidity and paresis of the upper and lower extremities.

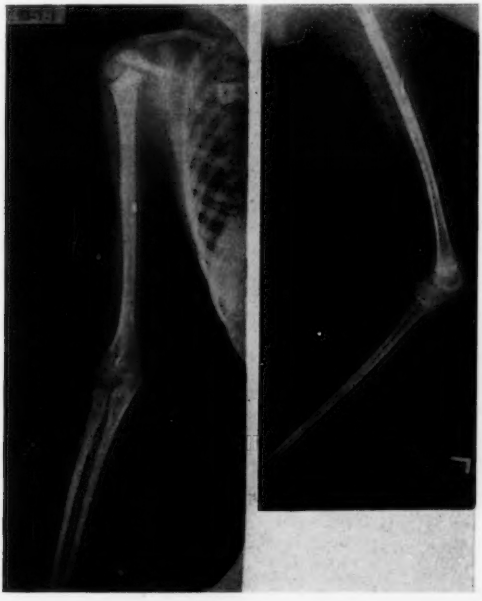

FIG. 2.—Soft tissue X-ray of patient D. D., demonstrating extreme wasting of muscles under subcutaneous fat.

*To illustrate article by J. Godwin Greenfield, Tillye Cornman, and G. Milton Shy.*

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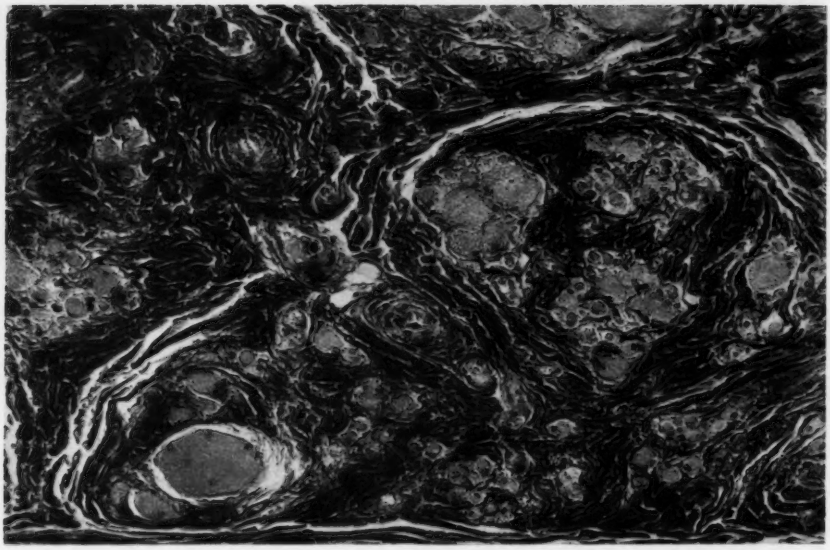

FIG. 3.—Infantile myopathy. A further section of a patient whose inflammatory response is seen in fig. 8. Note the profound endomysial collagen, the variance of muscle fibre size, internal nuclei, and absence of group lesions. (128–57, H.V.G., 240 times.)

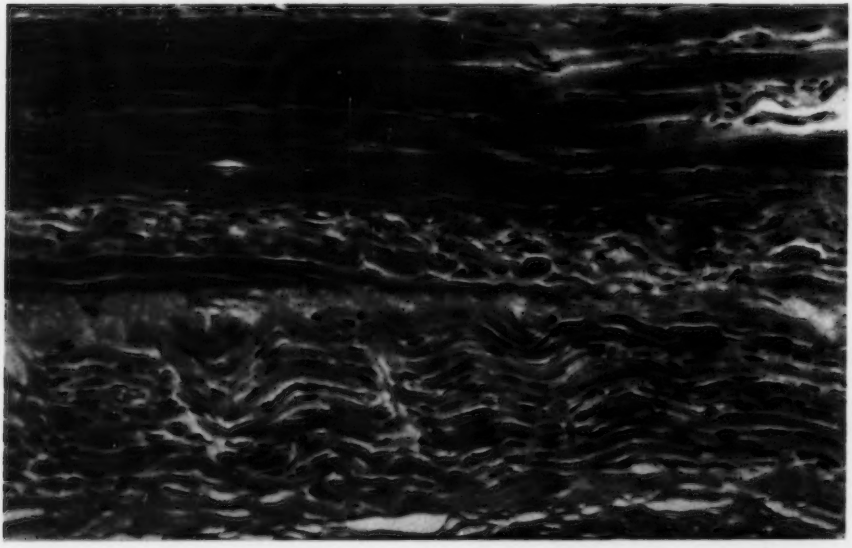

FIG. 4.—Typical longitudinal section of muscle removed from a patient with infantile spinal atrophy. Note the group lesions. (1077–B Gomori Trichrome, 250 times.)

*To illustrate article by J. Godwin Greenfield, Tillye Cornman, and G. Milton Shy.*

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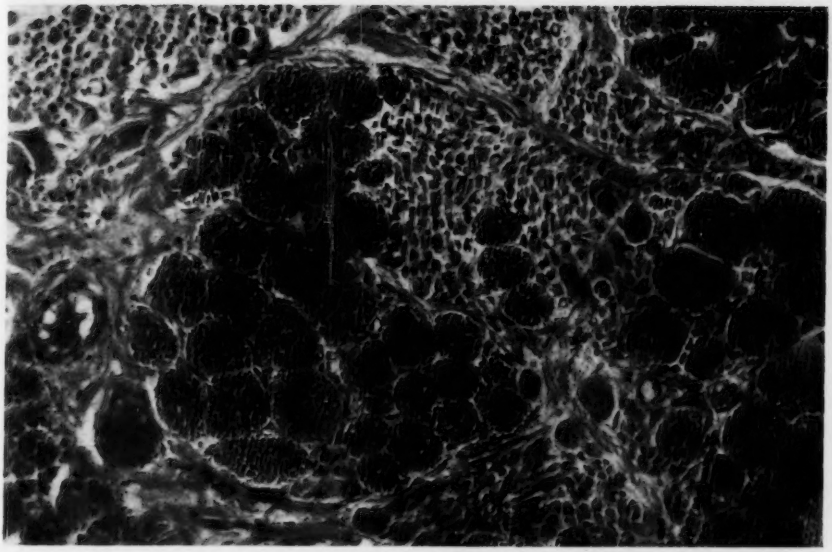

FIG. 5.—Cross section of a typical case of infantile spinal atrophy. (145–57 H. and E., 240 times.)

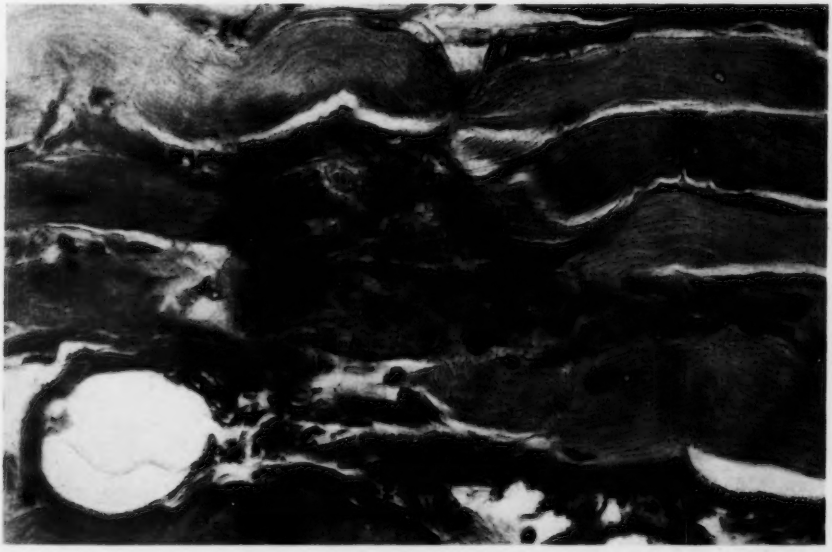

FIG. 6.—Infantile myopathy, demonstrating both cloudy fibres with loss of architecture and vesicular nuclei and prominent nucleoli, patient D. W. (1147–B, H. and E., 600 times.)

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PLATE LXII

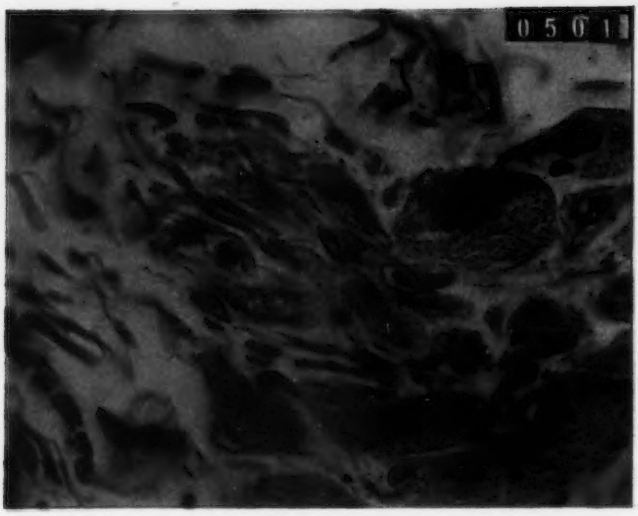

FIG. 7.—Infantile myopathy, showing a school of basophilic fibres with large vesicular nuclei and prominent nucleoli. (1147–C, H. and E., 750 times.)

FIG. 8.—Infantile myopathy in the youngest of two siblings. Note the presence of inflammatory cells adjacent to normal and damaged fibres. (128–57, H.V.G., 200 times.)

*To illustrate article by J. Godwin Greenfield, Tillye Cornman, and G. Milton Shy.*

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PLATE LXIII

FIG. 9.—"Central core" disease. Note the large fibre with two bundles of centrally placed myofibrils. The size of this fibre was 190 $\mu$. (13–56A Gomori Trichrome, 750 times.)

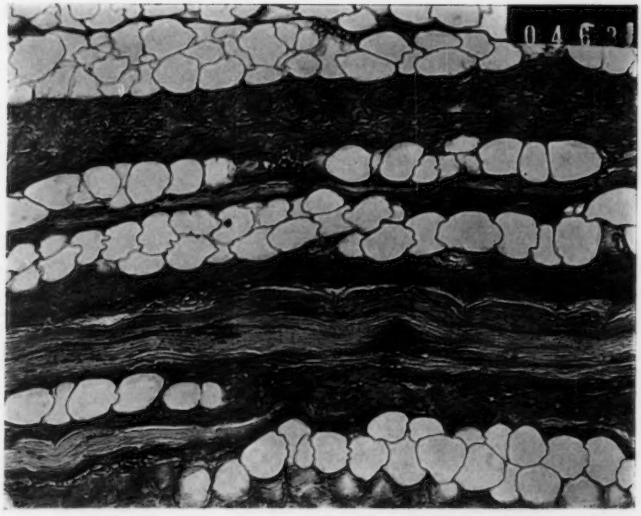

FIG. 10.—Infantile myopathy. The older sibling of the patient whose muscle appears in fig. 8. Note the large quantities of endomysial collagen and fat. (127–57 H.V.G., 150 times.)

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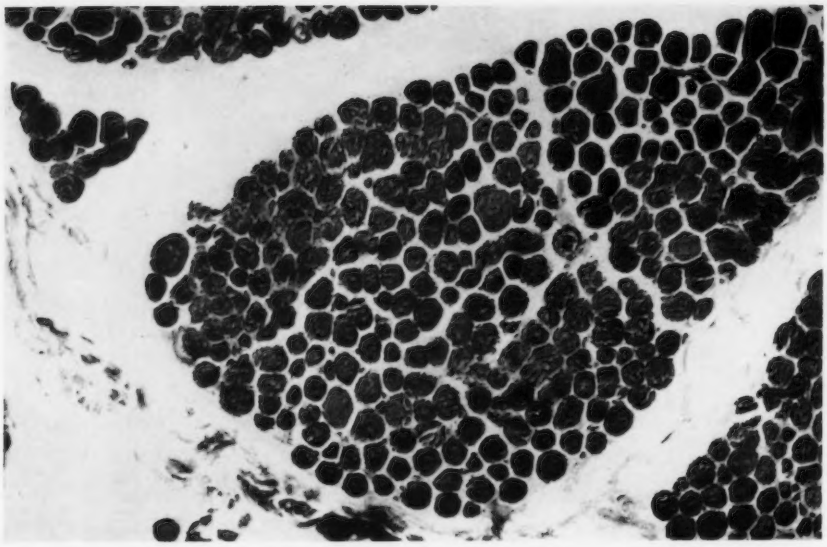

FIG. 11.—Benign congenital hypotonia, universally small fibres (13 to 18 $\mu$), with no architectural or connective tissue changes. Patient's age at this time was 3. (1077–B, Gomori Trichrome, 300 times.)

FIG. 12.—Arthrogryposis multiplex. The usual sitting posture of this patient, due to proximal muscle weakness and joint deformity.

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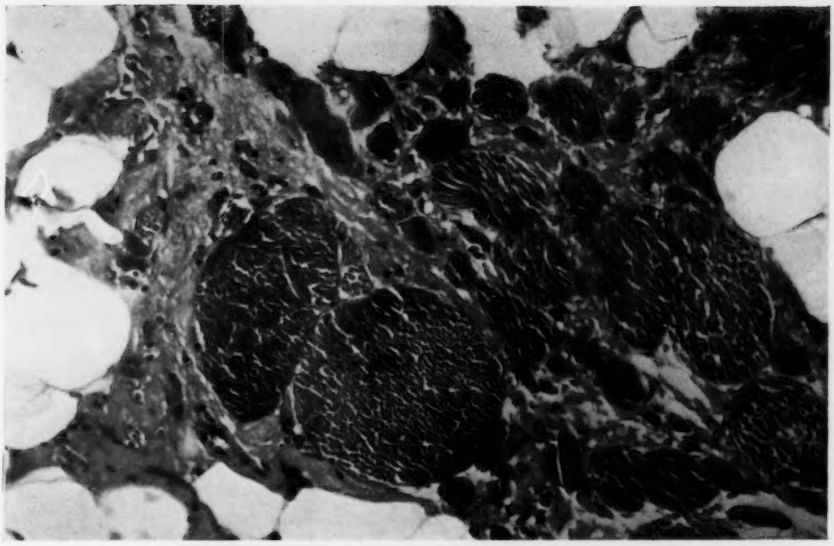

FIG. 13.—Arthrogryposis multiplex. Section of vastus lateralis. Note spectrum of muscle fibre size (large fibres, 180 $\mu$), internal nuclei, and increase in endomysial collagen. This would be consistent with myopathy. (140–56B, H. and E., 640 times.)

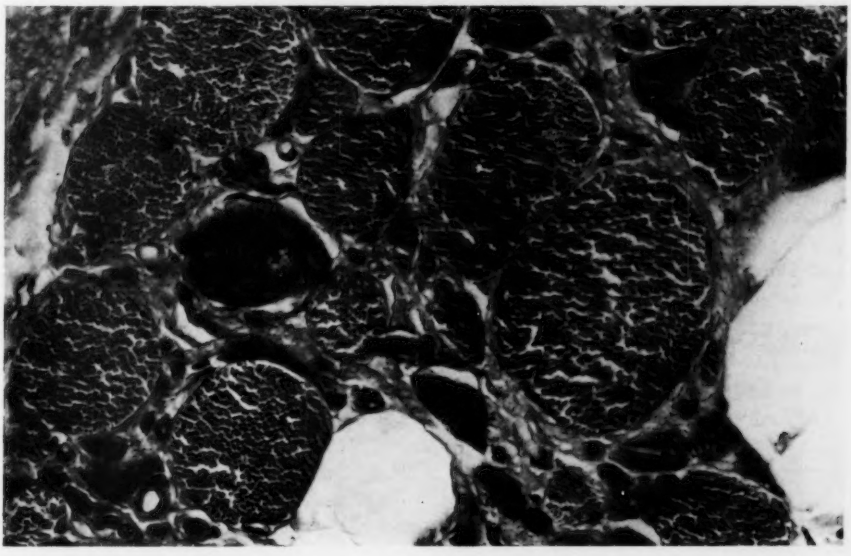

FIG. 14.—Arthrogryposis multiplex. Note large fibres, but also note the prominent blue fibre with vesicular nuclei, and prominent nucleoli, and but little fibrillary pattern. (140–56B, H. and E., 640 times.)

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PLATE LXVI

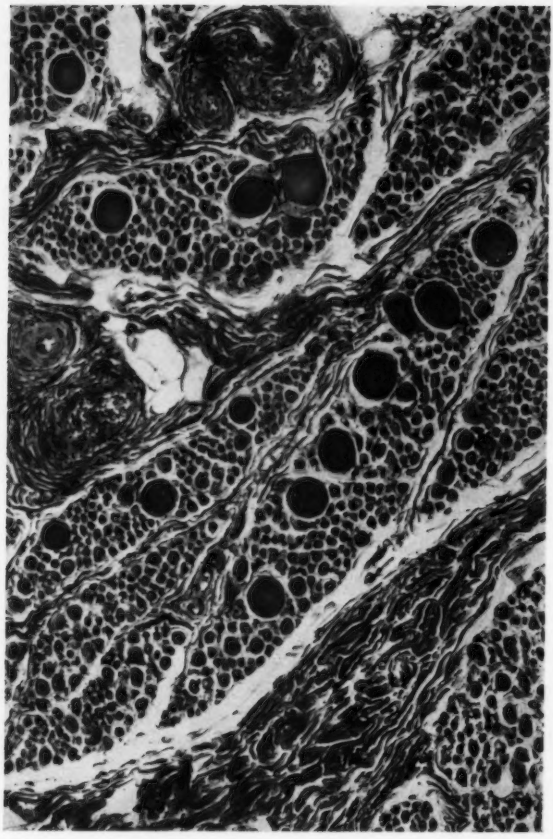

FIG. 15.—Infantile spinal atrophy, characteristic picture of large groups of small fibres and sparing of isolated normal or slightly enlarged fibres. Note the absence of endomysial collagen. (120–57, H. and E., 190 times.)

*To illustrate article by J. Godwin Greenfield, Tillye Cornman, and G. Milton Shy.*

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# ENDOGENOUS HYPOGLYCÆMIA[1]

BY

HUGH GARLAND

*The General Infirmary at Leeds*

FOUR hundred years ago Shakespeare attributed to John of Gaunt the epigram "Things sweet to taste prove in digestion sour" (Richard II). This was an astute observation on a type of hypoglycæmia which is only partially understood even now and still little known. Endogenous hypoglycæmia is a condition in which low blood sugar concentrations appear to be the primary cause of symptoms, but I only propose to discuss certain aspects. "Endogenous" is a more accurate term than "spontaneous," since there must always be a reason for the development of hypoglycæmia even if it cannot be fully explained. Despite extensive animal experimentation, clinical observation, and a welter of medical writings, the complete clinical picture—which is the aspect of greatest importance to the neurologist—has not yet been fully assessed. Because of the metabolic limitations which are peculiar to nervous tissue, the protean symptoms of hypoglycæmia fall predominantly into the neuro-psychiatric sphere; but hypoglycæmia is not a simple condition for clinical study nor an easy diagnosis to uphold and prove scientifically. Even in 1958, however, there is little "scientific" proof of many neurological diagnoses, this being especially true of disseminated sclerosis, and the neurological complications of cervical spondylosis and polyarteritis nodosa.

## PHYSIOLOGY

The activity and existence of the nervous system depend largely on the metabolism of glucose, but neural performance may remain normal despite a wide variation in the concentration of available glucose as determined by peripheral blood sugar measurements. Certain "normal" variations of blood sugar in relation to the fasting or post-prandial state are accepted, but the upper limits are extremely wide and very high figures, including those of severe diabetes, cannot be related to signs or to symptoms. The significance of low levels is even more dubious; their effects present many unsolved problems, and biochemical hypoglycæmia, like hyperglycæmia, often has no clinical counterpart.

[1]Presidential Address to the Section of Neurology, the Royal Society of Medicine, London, on October 2, 1958.



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Although any physician would regard certain blood sugar values as normal there are few biochemists prepared to state the normal range. One accepts that if the venous blood sugar is 150 mg. per cent two hours after a meal the patient is probably suffering from diabetes, but what constitutes an abnormally low level is by no means agreed; the figure of 70 mg. per cent is not regarded with suspicion, but most would feel that 60 is unusual and 50 abnormal, though the figures vary somewhat according to the method of estimation. There is no constant time-correlation between the clinical state and low blood sugar concentrations, and sometimes no correlation at all. A figure of 25 mg. per cent was once thought to be incompatible with life, but eleven years ago I saw a patient whose fasting blood sugar level was precisely that figure, who only suffered from occasional attacks of unconsciousness, and who achieved complete symptomatic relief by taking a high carbohydrate diet (fig. 1).

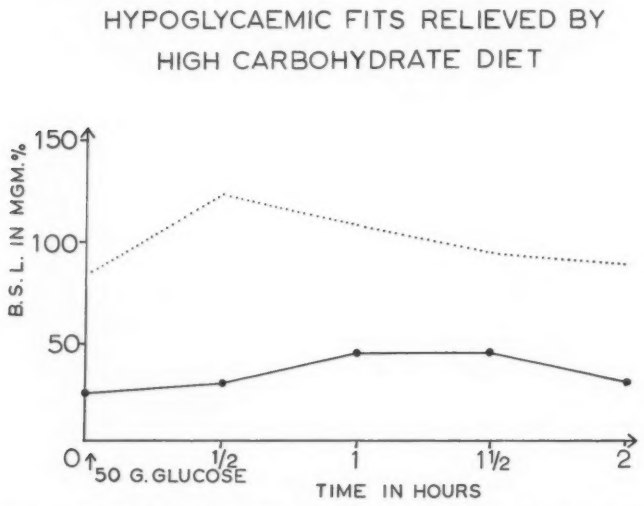


FIG. 1.—(In all illustrations the dotted line is an average normal curve.)

In children with the rare glycogen-storage disease of von Gierke, which is inherited as a Mendelian recessive, the blood sugar is always in the region of 60 mg. per cent or considerably less, and cannot be raised by injecting adrenaline; but they rarely show any evidence of cerebral dysfunction and are unlikely to come the way of the neurologist. Hyperinsulinism occurs in children, though often with little evidence of hypoglycæmic symptomatology, and blood sugar levels may be extremely low in infancy, especially in babies born of a diabetic mother, where compensatory islet hyperplasia arises to overcome the maternal hyperglycæmia (Farquhar, 1956).

The technique of estimating blood sugar has considerable bearing on the interpretation of figures. Most of my patients were examined in the Leeds General Infirmary where a modification of the Folin-Wu method, using venous blood, has always been used. The glucose-oxidase method, which is specific for glucose, will probably be more widely used in the future, and it may well show figures which are 20 mg. per cent lower at all levels. The diet taken during the few days preceding a glucose tolerance test is most important and if the carbohydrate intake has been reduced the test becomes completely unreliable (Conn, 1940*a*).

## ÆTIOLOGY

As neurologists, we are concerned with the signs or symptoms which result from hypoglycæmia as opposed to the incidental finding of low blood sugar levels in such disorders as Addison's disease, hypopituitarism, or gross liver damage. Presenting clinical endogenous hypoglycæmia may arise in three main ætiological groups, namely (1) as organic hyperinsulinism which results from the presence of a functioning pancreatic islet-cell tumour, (2) as a complication of gastric surgery, or (3) by predominantly psychological mechanisms. Apart from its therapeutic value, insulin has been used by the malingerer and has sometimes resulted in total pancreatectomy, though as far as I know this particular perversion has not been recorded in Great Britain. Insulin has also been used as a suicidal agent, and once at least in this country in the furtherance of murder (Birkinshaw, Gurd, Randall, Curry, Price and Wright, 1958). Insulin "reactions" in the diabetic and insulin "shock" treatment have been studied for more than a quarter of a century. The effects of exogenous hypoglycæmia do not always mimic the symptoms produced by the endogenous form and the manifestations of endogenous hypoglycæmia do not always follow the same pattern irrespective of the basic ætiology. Despite common nosological ground, the wide variation in the symptomatology of both exogenous and endogenous hypoglycæmia suggests that low blood sugar levels are not always the only, or even the main, factor.

*Organic hyperinsulinism.*—Though islet tumours, both adenomata and carcinomata (relatively 70 per cent and 30 per cent of proved examples), may well be as old as man himself, the earliest example recorded was in 1902 (Nicholls); and it was not until 1927, in the Mayo Clinic (Wilder, Allan, Power and Robertson), that the clinical diagnosis of organic hyperinsulinism was made and upheld at autopsy, nor until 1929 (Howland, Campbell, Maltby and Robinson) that the first islet adenoma was successfully removed in Toronto.

The islets of Langerhans contain *alpha* and *beta* cells with both histological and functional differences (Gomori, 1939); the *beta* cells are thought to secrete insulin, whilst the *alpha* cells produce glucagon, which possibly acts as an anti-insulin substance. The two types of cells can be

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identified histologically, but unfortunately this technique has rarely been applied to pancreatic tumours so that we cannot be certain whether they consist purely of *beta* cells or *alpha* cells, or both, though it has been known for many years that an islet adenoma may be "functioning" or "not-functioning" as regards the secretion of insulin. As far as I know there is no proved example of an *alpha*-cell tumour producing diabetes, though this would be a theoretical possibility. Similar *alpha* cells are found in the upper three-quarters of the gastric mucosa of the dog (Sutherland and de Duve, 1948) and if this is also true of man it might have the greatest clinical importance.

The precise mechanism whereby insulin secretion is normally controlled is complex. The islets may respond in step with the current blood sugar concentration, but if so there are many proved clinical anomalies. The average secretion of the adult pancreas is thought to be about 40 units per day, though this estimation is based on the results of total pancreatectomy, which must also remove a large number of *alpha* cells. Since many organs (and especially the brain) are constantly metabolizing glucose, it is probable that insulin is being continuously produced. We have no idea of the insulin output of an adenoma, but this could be much greater, or smaller, than that of the whole pancreas. Still less do we know what mechanisms govern the secretory function of the adenoma, which may well be autonomous. We do know, however, that the symptoms resulting from adenomatous activity may bear no relationship to the fasting state, or have any temporal association. But there may be a point in the evolution of a functioning adenoma when it provides all the insulin requirement of the body so that activity of the islets is in abeyance; this is suggested by the microscopic degranulation changes which appear in the *beta* cells of the remainder of the pancreas in the presence of an active adenoma but not if the tumour is inactive (Nerenberg, 1954). Low blood sugar concentrations may return to normal or even reach hyperglycæmic levels within a few minutes of the surgical removal of an adenoma (Garland, 1957*a*) but as far as I know permanent diabetes has never followed this procedure. In clinical assessment, we must also remember that an adenoma may sometimes cease to produce insulin, or that its secretory activity may remain static.

At the time of writing the number of proved examples of organic hyperinsulinism is probably not more than six or seven hundred, though 91 were seen in the Mayo Clinic between 1927 and 1953 (Breidahl, Priestley and Rynearson, 1956); but insulin "shock" therapy must have been given millions of times, considering that schizophrenia is the commonest diagnosis made on hospital patients at any given time, that most of these have had insulin therapy over the past twenty-five years, and that such treatment is carried out daily for several weeks. The observed effects of insulin treatment of psychotics show many similarities to organic hyperinsulinism, but also many differences, which may be

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determined in some way by the schizophrenic make-up. This does not apply, however, to patients suffering from psychoneurotic tension syndromes, in whom an injection of 100 units of soluble insulin is usually not followed by any symptoms.

So many laboratory aids are now available for confirmation of the diagnosis of hyperinsulinism that there can be little excuse for a futile abdominal exploration. Unsatisfactory operations have been not infrequent in the past, for three important reasons. The pancreas may look normal when in fact it is the site of diffuse, microscopic adenomatosis; an adenoma may be deeply buried in the head of the pancreas; and in 12 per cent there are multiple adenomata. The first of these problems calls for an immediate decision at the time of laparotomy, and provided the diagnosis has been established beyond reasonable doubt, the surgeon should be asked, if the pancreas appears normal, to remove the caudal half of the organ, which is a relatively easy procedure. I have no doubt that failure to carry out hemi-pancreatectomy is the main reason why the total number of recorded examples of islet adenomatosis only stands at 8 (Garland, 1957*a*). An adenoma in the head of the pancreas or multiple adenomata may still be overlooked but there is no method whereby the pre-operative differentiation between adenoma and adenomatosis can be made. Total pancreatectomy is a formidable operation and multiple explorations are undesirable. Perhaps unnecessary procedures might sometimes be avoided by the use of rapid frozen-section biopsies when the pancreas is macroscopically normal, since recorded examples suggest that adenomatosis, though not involving all the islets, is widespread (fig. 2A and B, Plate LXVII). If such a biopsy shows no abnormality the possibility of ectopic adenomata must also be kept in mind; these are as infrequent as adenomatosis but are occasionally found in adjacent structures.

Even when the diagnosis of hyperinsulinism has been adequately confirmed, laparotomy may be undesirable or impossible, and I have known 3 patients in this category. A middle-aged man refused operation. A woman of 75 was considered too old for surgery unless other methods failed, and a child of 4 was thought to be too young. All 3, and others in whom the diagnosis was less certain, responded very well to dietetic treatment. Hyperinsulinism can be controlled wholly or partially by a high-carbohydrate diet, and, though the rationale is based on the unproved assumption that the patient is being constantly subjected to an abnormally high secretion of insulin, which may be counterbalanced by the excessive ingestion of carbohydrate, the clinical results are often conclusive. There is great confusion about the dietetic treatment of hypoglycæmia. Conn has written prolifically on this subject over the past twenty years. In 1940 he described the value of a high-carbohydrate diet in organic hyperinsulinism, and of a high fat, high-protein and low-carbohydrate intake in the treatment of "functional" hypoglycæmia (Conn, 1940*b*).

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But many writers since then have used the latter diet in treating organic hyperinsulinism without explanation (Cohen, 1950; Breidahl, Priestley and Rynearson, 1956). My own experience supports Conn's views. The advantage of a high carbohydrate diet, apart from the relief of symptoms, is its cheapness; the disadvantage is the resulting obesity, especially if surgical intervention becomes unavoidable. It must be emphasized, however, that although the continuous dietetic treatment of hypoglycæmia depends on the ætiology, immediate relief of symptoms may be obtained by taking glucose.

How is the diagnosis of hyperinsulinism to be established? The appropriate investigations will obviously not be carried out unless the diagnosis is suspected on the basis of the clinical history, and occasionally on the physical signs. Unfortunately all the diagnostic aids have rarely been applied to proved examples, and for this reason the significance of the various investigations is not clearly defined. Whipple's triad (Whipple, 1938) for the diagnosis of organic hyperinsulinism was a

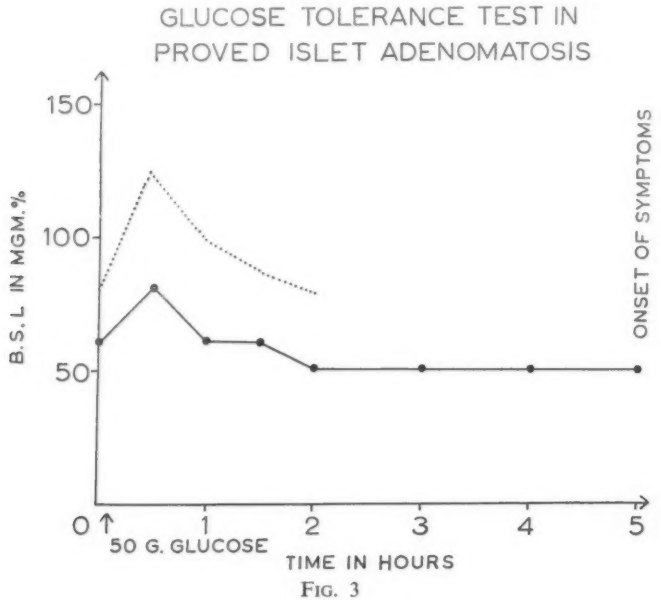


FIG. 3

valuable clinical advance; it stated that the fasting blood sugar level should be persistently low, that attacks of some kind, obviously resulting from disordered cerebral function, occurred in the fasting state, and that these attacks could be rapidly relieved by taking glucose. Although this is still a useful guide, it is not always strictly true, for my patient (Garland, 1957*a*) with adenomatosis, who had suffered from attacks of

automatism with amnesia for several years, had never had symptoms in the fasting state, and had repeated fasting blood sugar concentrations of 60 mg. per cent or more. During a glucose tolerance test on this patient (fig. 3) the peripheral blood sugar was maintained steadily at 50 mg. per cent and it was not until the end of 4 hours that symptoms appeared, and then rapidly. Many test-tube-minded physicians will be shocked at the serious and authoritative suggestion that the glucose tolerance test plays no part in the diagnosis of hyperinsulinism (Breidahl, Priestley and Rynearson, 1956; Richardson and Hill, 1957), but this heresy has considerable practical backing. In many patients with proved hyperinsulinism (including some of my own) a glucose tolerance test has been normal. More often the fasting blood sugar level is obviously low and the curve tends to be flat or it may even be inverted; but fig. 4 shows a low fasting level with return to normal values in a patient from whom an islet adenoma was later removed. Fig. 5 is the glucose tolerance

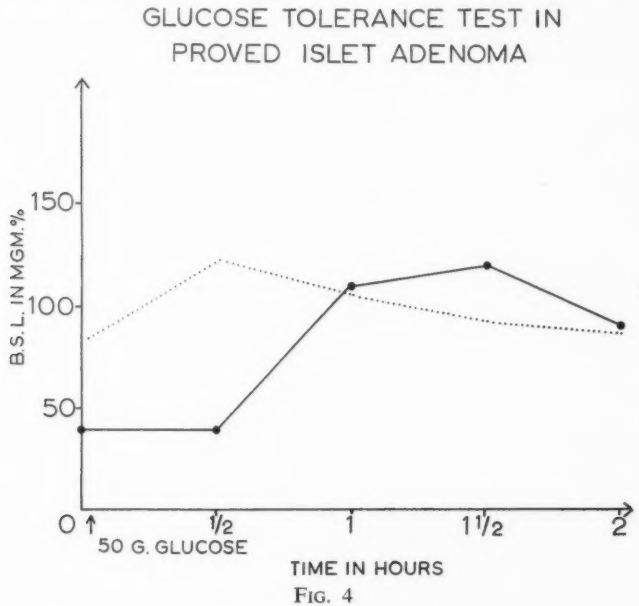


FIG. 4

test carried out two days after severe neurological symptoms in an old lady. Many physicians would reject the possibility of hypoglycæmia on this particular test, but in a later attack she was found to have a blood sugar level of 40 mg. per cent, and her symptoms were immediately reversed by adrenaline. Since that episode, six years ago, she has taken a high carbohydrate diet and has remained symptom-free. Random fasting blood sugar estimations are not always helpful, but abnormalities

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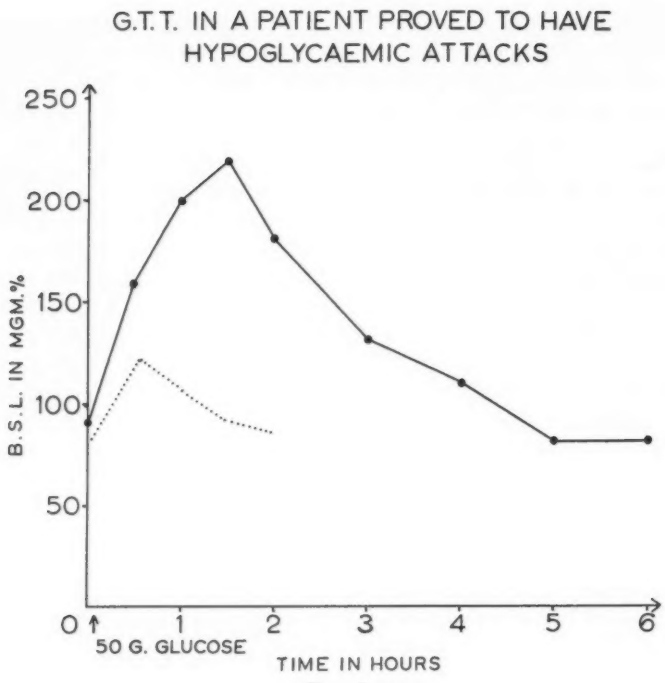


FIG. 5

may be aggravated by twenty-four to seventy-two hours' starvation, especially if this be followed by vigorous exertion, though such investigations are not likely to be of much value unless they precipitate symptoms of the appropriate kind. Even when the patient is suffering from hypoglycæmic symptoms there is no constant relationship between the concentration of the peripheral blood sugar and cerebral function. The finding of a level of 50 mg. per cent or less is highly suggestive of a hypoglycæmic ætiology, and 30 mg. per cent is almost diagnostic of organic hyperinsulinism, though a normal level when symptoms appear by no means excludes the diagnosis. The opportunities for such tests rarely occur, but despite all the difficulties many patients have had successful surgical treatment on the basis of blood sugar estimations alone.

If symptoms result intermittently from hyperinsulinism they might be precipitated by the injection of insulin. This has been proved, as little as 5 units in the fasting state reproducing the original symptoms in a patient from whom an islet adenoma was later removed (Fraser, Maclay and Mann, 1939). Moreover, observations of the greatest importance in relation to post-operative and psychosomatic hypoglycæmia were

made by this method in the same patient; time-correlation of blood sugar concentration with the clinical state showed that if the fall was rapid symptoms occurred at about 70 mg. per cent, although much lower levels were not associated with symptoms if the fall was slow. Because the manifestations of hypoglycæmia may be not only unpleasant but also sinister, and because hypoglycæmic coma may quickly become irreversible, such a diagnostic test should only be carried out under the strictest supervision. But symptoms produced by insulin are rapidly relieved in the early stages by glucose, and the giving of insulin to such patients is no more ethically questionable than starvation with or without exercise. I feel, therefore, that we should always apply the full diagnostic battery before any patient is subjected to surgical procedures.

Other methods of investigation include the intravenous glucose tolerance test (which I have never used) and the "loaded" oral glucose tolerance test. Personal experience of the latter, using 300 grammes of glucose, has not been helpful because the patients frequently vomit (which happens occasionally with the usual dose). There is little proof that more than 50 grammes is necessary to produce an adequate hyperglycæmic stimulus.

Bioassay of the plasma insulin concentration by a complex technique using rat diaphragm has shown high insulin levels in the presence of an adenoma, and a rapid fall to normal after its removal. This method has only been used in a few centres (Vallance-Owen and Hurlock, 1954) and its complete reliability may not yet be proved beyond doubt. Perhaps a more simple assay will be the estimation of insulin-like activity using rat adipose tissue (Martin, Renold and Dagenais, 1958).

Electro-encephalography may play a diagnostic role; it has been both totally disparaged (Breidahl, Priestley and Rynearson, 1956) and strongly advocated (Laidlaw and Rab, 1957). The EEG changes in hypoglycæmia are non-specific, only reflecting a depression of cerebral metabolism, and they must be considered in relation to both symptoms and blood sugar concentrations at the time of recording. Increasing hypoglycæmia causes disappearance of the *alpha* rhythm and later *theta* and *delta* waves appear, though there is no critical level at which these changes invariably occur. The clinical picture can be more closely correlated with the simultaneous electrical changes than with the simultaneous blood sugar level (Wyke, 1952). EEG changes mirror the clinical state or perhaps anticipate it (Brazier, Finesinger and Schwab, 1944), just as biochemical hypoglycæmia may precede considerably the appearance of clinical manifestations, although both may be unassociated with symptoms. EEG abnormalities in hypoglycæmia may be provoked by overbreathing and may be reversed by giving oral glucose even though the patient is making no complaints, and this finding may be very important.

Whether hypoglycæmic symptoms arise "spontaneously" or from cold-blooded iatrogenesis, the most valuable diagnostic test must be their

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reversal by glucose, the route depending on the patient's state of consciousness. They may also be reversed by adrenaline or ephedrine, but neither is as reliable as glucose and should not be used unless the patient is in coma, when the administration of nasal or intravenous glucose may be impracticable.

*Hypoglycæmia complicating gastric surgery.*—Post-prandial symptoms resulting from gastric operations have been known for more than forty years. In the earlier part of the century the common surgical procedure of gastro-enterostomy was always potentially reversible. More recently there have been variable waves of enthusiasm for the irreversible procedures of gastrectomy (partial or total) and vagotomy. These operations may all determine hypoglycæmia with clinical manifestations which fall into two groups with both clinical and ætiological differences. In the first group the patient feels faint within minutes of taking food because a meal of high carbohydrate content, which is hurried into the jejunum, produces a sharp fall in blood volume by osmotic mechanisms. This is rapidly reversed, but is closely related to the appearance of symptoms and electrocardiographic changes, and constitutes the "early dumping syndrome" (Medwid, Weissman, Randall, Bane, Vanamee and Roberts, 1956). Such episodes are largely abolished by reducing the carbohydrate intake, and taking meals of high-fat and high-protein content. In the second group, symptoms which may be serious appear one to two hours after food. The mechanism is not yet fully understood, though we know that after gastric operations, and particularly gastrectomy, there is sometimes a permanent disturbance of glucose metabolism. In these patients the glucose tolerance test shows a reactive type of curve; the fasting blood sugar level is normal but there is a rapid rise to an abnormally high figure, which is followed by a rapid fall either to normal or to hypoglycæmic levels, the lowest figure I have seen being 30 mg. per cent. If symptoms arise, they may be determined by low blood sugar concentrations or, perhaps more often, by the rapidity of the fall, which may be 100 mg. per cent or more in half an hour. The reactive type of glucose tolerance curve has usually been thought to result from the sudden absorption of a large amount of glucose which stimulates excessive secretion of insulin by the pancreatic islets. Such a view is supported by the time-lag between taking food and the appearance of symptoms, and by the undoubted improvement which follows the reduction of carbohydrate intake. But this theory does not explain why these syndromes only occur in a small proportion of patients, and other factors must be considered. There are presumably no important mechanical differences between one vagotomy and another, though there are various methods of performing gastro-enterostomy, and still more variability in the technique of gastrectomy. Symptoms are more likely to arise in people with a pre-operative neurotic make-up, and there are many points of similarity between this group and the psychosomatic

type of hypoglycæmia. But another factor which has not yet been assessed may be all important—namely the possible removal during gastrectomy of *alpha* cells which may determine a decreased secretion of glucagon. None of these theories, except perhaps that of psychogenesis, accounts for the fact that there is almost invariably an interval before the appearance of symptoms, which may be as long as thirteen years. A sudden dietary indiscretion is unlikely to be the explanation of symptoms appearing after this latent interval, though I have seen 2 patients in whom hypoglycæmic syndromes were apparently precipitated in the fasting state by alcohol. One of these had had a subtotal gastrectomy ten years previously and on three occasions alcohol rapidly produced symptoms, once in the form of prolonged coma. The other, thirteen years after gastro-enterostomy, had a long phase of automatism with patchy amnesia. Both showed glucose tolerance curves of the reactive type, with hypoglycæmic levels; the second had taken only a moderate amount of alcohol, and the first a homœopathic quantity—judged by anybody's standards. I have tried to reproduce symptoms in this way, to the satisfaction of the patient but without the advancement of clinical science, though there is experimental evidence that alcohol can depress cerebral metabolism *in vivo* (Thompson and King, 1957).

Unfortunately there have been few extensive glucose tolerance studies after gastric operations, and I am not familiar with any investigation of glucose metabolism before and after operation. In the largest series, from Glasgow (Muir, 1949), tests were carried out on 86 patients after subtotal gastrectomy. Of these, 52 were normal; many of the others showed reactive curves sometimes reaching 300 mg. per cent within an hour. 6 patients showed hypoglycæmic symptoms two hours after food, the latent period varying from three to seventeen months. I have recently done glucose tolerance tests before and after partial gastrectomy on 8 patients; there has been no change in the shape of the curve and only a slight general lowering of blood sugar levels after operation (though 50 mg. per cent appeared several times) with one striking exception (fig. 6): this remarkable post-operative glucose tolerance test was carried out four months after a partial gastrectomy, when the patient was doing heavy work, on a normal diet, and entirely free from symptoms.

Establishing the diagnosis is more difficult in the post-operative group than in the first; indeed these syndromes have frequently been overlooked because neither physician nor surgeon has considered that transient neuro-psychiatric disturbances could be related to a previous gastric operation. When it is thought that symptoms may be of this ætiology, no matter how remote the operation, a prolonged glucose tolerance test lasting six hours may be suggestive. Personal attempts to precipitate symptoms in such patients by small doses of insulin have failed. As in organic hyperinsulinism symptoms can be quickly relieved by taking

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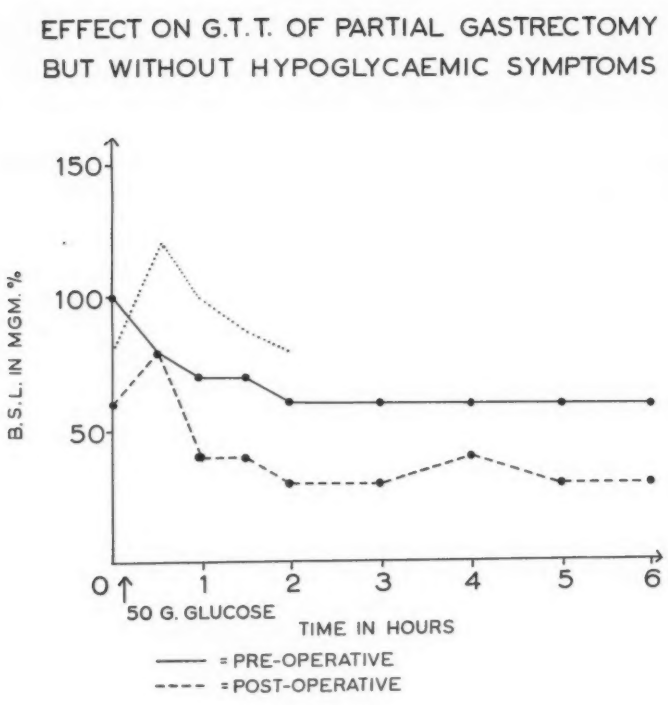


FIG. 6

glucose at an early stage, or by the injection of adrenaline, and the value of giving the patient a low carbohydrate, high fat, high protein diet as a therapeutic test is, in my experience, unquestionable.

*Psychosomatic hypoglycæmia.*—The term "psychosomatic" is preferable to "functional" or "nervous" hypoglycæmia for obvious reasons. Some observers consider psychogenesis to be much the commonest cause of endogenous hypoglycæmia (Conn and Seltzer, 1955) but this has not been my experience. The diagnosis is even more difficult to confirm than in the first two groups and is usually only made when a patient with a number of neurotic symptoms describes transient events which have a remarkably "organic" stamp—for example, sudden attacks of unconsciousness which are obviously neither syncopal nor hysterical. Again the prolonged glucose tolerance test may be helpful, as well as the therapeutic trial of a high-fat, high-protein diet, or the rapid reversal of symptoms by glucose.

The mechanism is thought to simulate that of the post-operative group, gastro-intestinal hurry (which can undoubtedly be determined by psychogenesis) resulting in rapid and excessive absorption of glucose.

In some of these patients there is a reactive glucose tolerance curve like that seen after gastric operations, but often the usual smooth rise and fall is changed into a series of oscillations during which unusually low figures may be reached; in others oscillating levels may follow an initial reactive peak (figs. 7 and 8).

In the treatment of psychogenic tension states, provided normal meals are taken, most patients will tolerate an injection of 100 units of soluble insulin on waking, and will develop no symptoms other than increased appetite and sweating. Of 45 patients treated by this method only 2 were unable to tolerate 100 units. 4 developed symptoms after 100 units though never on the first day this dose was given. One became unconscious on the third day, another became confused, with auditory hallucinations, on the tenth day; the third had a visual hallucination of a large, red, stationary sphere with a green halo, which persisted for ten minutes, and the fourth only became mildly drowsy. The rarity of symptoms is remarkable when one considers fig. 9 which shows the fluctuations in blood sugar levels during the course of the day in 5 of these patients. This is comparable with the treatment of schizophrenia, where coma has been known to follow as little as 15 units of insulin yet has failed to appear even after 1,000 units, though the important difference is that schizophrenic patients are starved until coma ensues. In the deliberate production of insulin coma there is also a remarkable

PSYCHOSOMATIC HYPOGLYCAEMIA
WITH OSCILLATING LEVELS

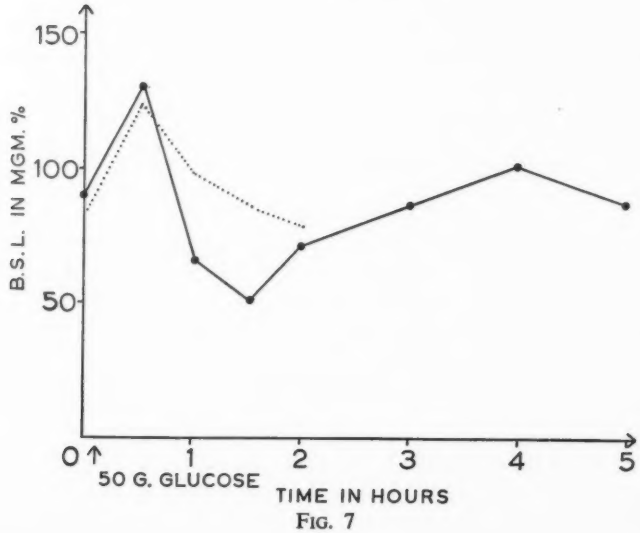


FIG. 7

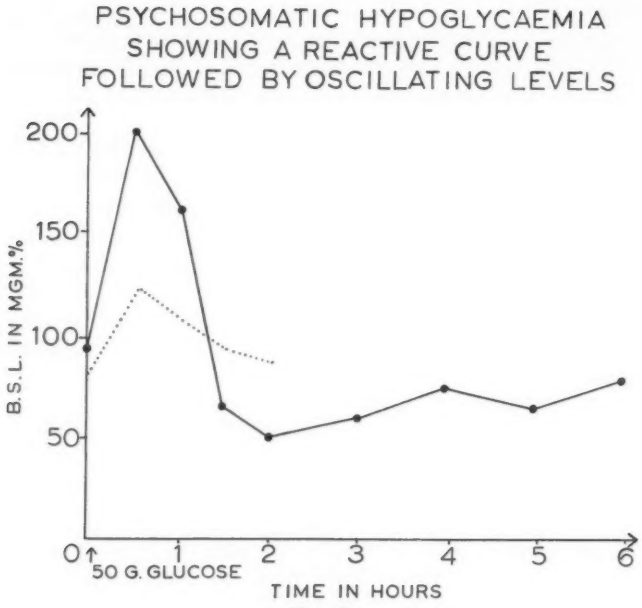


FIG. 8

variation in blood sugar concentration, patients sometimes being conscious at a level of 25 mg. per cent, or in coma at 60 mg. per cent, though they are usually in a state causing alarm if the figure has fallen to 15 mg. per cent. But twenty years ago it was observed by Sakel (1939) himself that the clinical condition bore little relationship to the simultaneous blood sugar level.

In the past twelve years I have made a diagnosis of clinical hypoglycæmia in 36 patients, rightly or wrongly, and their distribution in the three main ætiological groups is shown in fig. 10.

## NEUROLOGICAL MANIFESTATIONS

Although the normal range of blood sugar is somewhat nebulous, major departures from "normal" in either direction may have profound effects on the central nervous system. The *central* nervous system is emphasized because there are no proved direct effects of hypoglycæmia on the cranial or peripheral nerves. Both hypoglycæmia and diabetes may involve the spinal cord, though there are vivid differences between the effects of these conditions on the brain and on the cord. Diabetes may cause coma, which is determined by aceto-acetic acid rather than glucose, but there are no proved examples of chronic diabetic encephalopathy comparable, for example, with diabetic retinopathy. Hypoglycæmia may also cause coma, which may be irreversible or may

BLOOD SUGAR LEVELS IN NORMAL SUBJECTS FOLLOWING 100u. SOLUBLE INSULIN

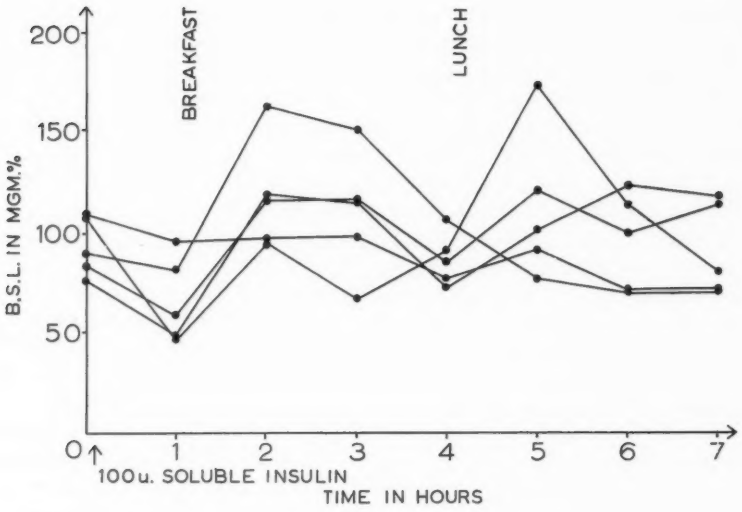


FIG. 9

CLINICAL HYPOGLYCAEMIA

| AETIOLOGY | MALE | FEMALE | TOTAL |
|---|---|---|---|
| HYPERINSULINISM | 6 | 5 | 11 |
| POST-OPERATIVE | 11 | 4 | 15 |
| PSYCHOSOMATIC | 4 | 3 | 7 |
| MISCELLANEOUS | 1 | 2 | 3 |
| TOTAL | 22 | 14 | 36 |

FIG. 10

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be followed by permanent brain damage, but there are no progressive forms of hypoglycæmic encephalopathy, excluding the additive effects of recurrent damaging episodes. Conversely diabetes and hypoglycæmia may both produce slowly progressive and not dissimilar forms of amyotrophy, whether this be of central or peripheral origin, but neither condition produces an *acute* cord syndrome (Williams, 1955; Garland, 1957*b*). These differences may be determined phylogenetically.

The glucose demands of the brain vary from one person to another, and from time to time in the same individual. Although the glucose requirements of different parts of the cerebrum vary, so that hypoglycæmia may effect one part of the brain more than another, we might expect hypoglycæmic syndromes to be at least bilateral if not strictly symmetrical, but for some unexplained reason this is not so.

Some of the early and well-known symptoms of over-dosage with insulin, particularly vague sensations of weakness and anxiety, sweating, palpitation, pallor and nausea, are probably determined by the release of adrenaline. These have all been observed frequently in endogenous hypoglycæmia and, apart from disturbances of consciousness, are the most common symptoms in all ætiological groups. They are of great importance and may give the first clue to the diagnosis.

In all the patients in whom I have made a diagnosis of endogenous hypoglycæmia there has been some disturbance of consciousness, apart from 2 with purely amyotrophic syndromes. "Disturbance of consciousness" covers as wide a nosological range as in any other context; it is impossible to list these "dysconscious" states in terms of quantitative or qualitative change, and only some of the more striking aspects will be mentioned. One of the simplest phenomena is for the patient to pass through a phase, lasting for seconds, minutes or hours, during which his behaviour appears to be normal or only slightly disturbed, but for which he later has total amnesia. This resembles the hysterical fugue, though there are two important differences. In the fugue the patient's behaviour will be obviously pathological in retrospect, and the amnesia can always be recovered by various diagnostic tricks; in the hypoglycæmic state behaviour may be apparently normal, though perhaps inappropriate, but the amnesia is permanent and comparable with the post-traumatic state of head injury. In patients with organic hyperinsulinism, but not in the other groups, difficulty in waking in the morning may be an early symptom even though there are no other immediate sequelæ. In all types of endogenous hypoglycæmia attacks of bizarre behaviour, usually with amnesia, are frequent; in these the patient may be confused, often noisy, dysarthric, ataxic, apparently drunk, and even violent. No matter what the basic cause, most of the patients recorded have had their symptoms for years and they have usually been under treatment for "neurosis" or "psychomotor epilepsy." Complete loss of consciousness may take various forms. The onset of coma may

be sudden or gradual, and it may be transient, protracted, or irreversible. In some patients coma is associated with major epilepsy which is indistinguishable from that produced by any of the other multitudinous causes of this symptom. In others phases of coma may not be punctuated by convulsions. Here a parallel may be drawn with the effects of insulin therapy which is occasionally associated with convulsions in the early stages and sometimes when the deepest coma has been produced. Although epilepsy in many forms frequently occurs in the hypoglycæmic state without preceding stupor or coma, it is a curious fact that *status epilepticus* virtually never arises.

The development of irreversible coma has always been a known danger of insulin therapy and for this reason it is usual to allow deep coma to last for only a few minutes. Irreversible coma resulting from endogenous hypoglycæmia is also of the greatest importance, and many people have died from an insulin-producing tumour when the diagnosis has not been established sufficiently early, for three reasons. Blood sugar estimations may never have been made because the coma was thought to result from some form of intracranial disease; low blood sugar levels have often been observed but ignored; and, in hypoglycæmic coma, blood sugar concentrations may be normal or even in the hyperglycæmic range (Richardson and Russell, 1952). We do not know how long a patient can remain in coma before this state becomes irreversible, but personal experience suggests that after as long as a week there may be "spontaneous" resolution. On the other hand I have seen coma which was found to be hypoglycæmic within thirty-six hours, and appropriately treated, terminate fatally a month later.

An important lesson one presumably learns from this experience is that unexplained coma should always be treated with intravenous glucose and especially when the previous history is not available; since diabetic coma will have been eliminated I doubt whether this therapeutic test could ever be contra-indicated.

Histological studies show "anoxic" changes, particularly in the cerebral cortex, the basal ganglia, and the cerebellum, and the results of transient disorders arising at these anatomical or physiological levels are clearly seen in non-fatal examples.

Temporary or recurrent dysphasia, hemiparesis and homonymous hemianopia have frequently been observed as hypoglycæmic phenomena, and in one of my patients there was a hemiplegia associated with simultaneous contralateral choreo-athetosis. Occasionally paralyses or dementing states have become permanent, but irreversible neurological syndromes are never progressive and only result from a transitory phase of hypoglycæmic cerebral anoxia which produces neuronal damage.

Disturbances of vision are frequent. Diplopia, with or without squint, is often a premonitory symptom of a hypoglycæmic confusional state and is a not unusual complaint during the early stages of insulin



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therapy, in those patients capable of remembering their experiences. Macropsia, micropsia, chromatopsia and more complex visual hallucinations, sometimes resembling those of mescaline intoxication, have also been observed; the patho-physiological basis is unknown though such disorders probably arise from temporal lobe dysfunction. Olfactory hallucinations and parosmia may also arise.

Rotatory vertigo of hypoglycæmic origin has been an important discovery, especially as this may be the only clinical manifestation of endogenous hypoglycæmia (Moorhouse, 1956). In my experience the patients usually complain of the sudden onset of dizziness with a rotatory element, either subjective or objective, sometimes coming on so precipitately that they fall to the ground, and often associated with nausea and vomiting. The duration of the vertigo usually varies from a few minutes to about an hour, though occasionally it has been more prolonged. I have not had the opportunity of examining any of these patients during an attack, but in none was there concomitant deafness or tinnitus, suggesting that function is disturbed at a non-labyrinthine level. Vertigo frequently arises during insulin therapy, and many patients are observed to be ataxic several hours after coma has been terminated. Analogy with visual and auditory hallucinations, as well as with observations during cortical stimulation in the conscious patient (Penfield and Rasmussen, 1950), make it probable that rotatory vertigo also results from a disturbance of function in the temporal lobes. Further weight is lent to this view by the finding of maximal or asymmetrical electroencephalographic changes in the temporal region during hypoglycæmia (Garland, 1957*a*) and by histological confirmation of "anoxic" damage which may be most severe in the temporal cortex, including Ammon's horn. I am not familiar with permanent or even temporary blindness, deafness, loss of the senses of smell or taste, or of phasic depression, resulting from hypoglycæmia. Narcolepsy and cataplexy, however, may be associated with low blood sugar levels and then the clinical syndrome and the biochemical deviations are probably both the result of hypothalamic dysfunction; even so dietetic restriction may be of therapeutic value in a syndrome which is often very resistant to medicinal treatment.

All the transient disturbances resulting from hypoglycæmia tend to be accompanied by excessive sweating and are sometimes followed by excessive hunger; headache and vomiting are not infrequently associated.

Many people must have died in hypoglycæmic coma resulting from organic hyperinsulinism, but I am not aware of death from post-operative hypoglycæmia though I suspect that this variety may cause prolonged, and possibly irreversible, coma; psychosomatic hypoglycæmia appears to be the least sinister form, and is only potentially fatal.

Hypoglycæmia may determine a clinical picture simulating that of motor neurone disease, but this is not likely to be recognized unless the picture of widespread muscular weakness and wasting, with fasciculation

or other accompaniments, is interspersed by episodes of disturbed consciousness (Williams, 1955). The diagnosis of motor neurone disease should perhaps never be made until adequate tests for organic hyperinsulinism have proved to be negative. It may well be that, if not treated, hypoglycæmic amyotrophy can be fatal. I have not been able to establish this diagnosis myself though I have at present under observation two suspected patients (fig. 11). The scanty references to proved examples of hypoglycæmic amyotrophy make it fairly certain that this syndrome is frequently overlooked, usually being dismissed as motor neurone disease. As far as is known hypoglycæmic amyotrophy is only produced by organic hyperinsulinism; appropriate surgical treatment can certainly arrest the process or even reverse it.

## Conclusions

Innumerable observations have been made on all forms of hypoglycæmia by neurologists, psychiatrists, biochemists, and even general physicians, and many conclusions are incontrovertible. In spite of this, however, my feeling is that we are still only on the fringe of knowledge, especially regarding endogenous hypoglycæmia. Many examples are overlooked because the diagnosis is never considered. Abdominal operations are carried out needlessly on inadequate criteria, or are failures through lack of diagnostic panache. Scientific proof often escapes us, but clinical impression and the undoubted value of appropriate dietetic therapy can

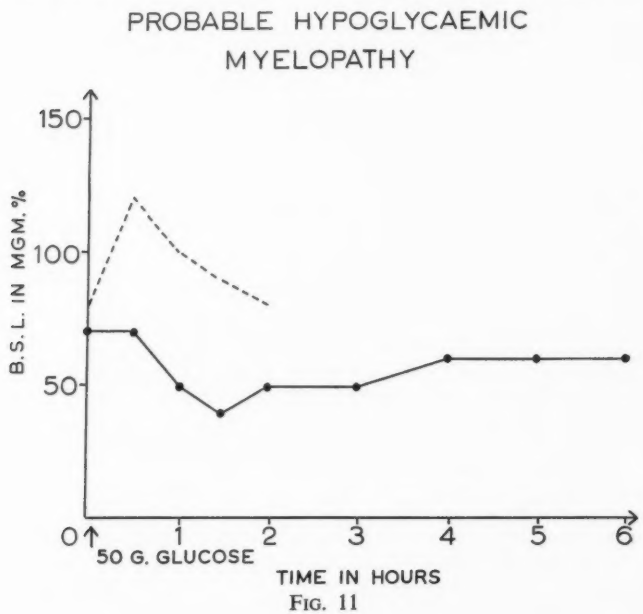


Fig. 11

still reduce the considerable morbidity and, it may be, mortality. In this condition, as in many others, laboratory aids, though frequently invaluable, may prove to be both a clinical snare and an academic delusion.

ACKNOWLEDGMENTS

I should like to thank Professor G. H. Lathe for his valuable advice; several surgical colleagues for allowing me to carry out pre- and post-operative glucose tolerance tests; Dr. T. W. Sutherland for the histological studies; my ex-house physicians Dr. Pamela Barker and Dr. Lois Gendall for producing the illustrations; and, especially, Dr. Doreen Moorhouse who has allowed me to draw freely on her thesis for the M.D.(Leeds) and given other advice and criticism.

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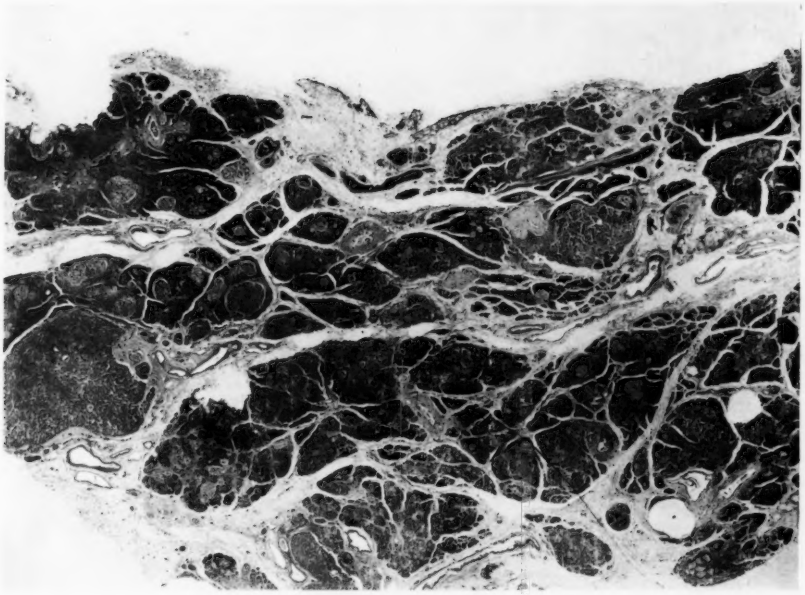
PLATE LXVII



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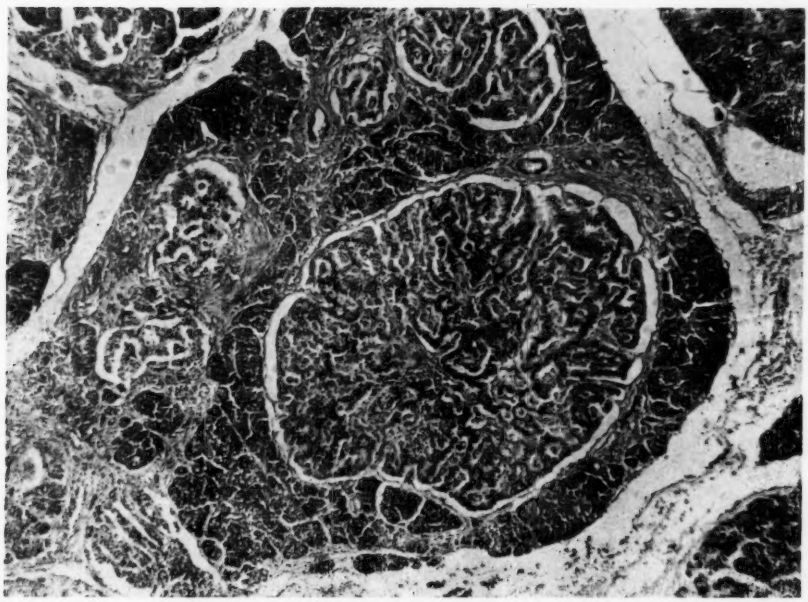

B

FIG. 2.—Pancreatic adenomatosis (haematoxylin and eosin A × 10, B × 70).
*To illustrate article by Hugh Garland.*

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# SOME AUTONOMIC CONCOMITANTS OF ICTAL AUTOMATISM

## A Study of Temporal Lobe Attacks

BY

J. M. VAN BUREN

*(From The Branch of Surgical Neurology, National Institute of Neurological Diseases and Blindness, National Institutes of Health, U.S. Public Health Service, Department of Health, Education and Welfare)*

### Introduction

Curious spells in which a man may wander about in confusion and exhibit the disordered function of the autonomic nervous system must have been known since ancient times and were well described over four centuries ago by Benivenius (Temkin, p. 179, 1945). In a series of papers, Jackson and his associates (Jackson and Beevor, 1889; Jackson and Colman, 1898; Jackson and Stewart, 1899) demonstrated the relationship between seizures of this kind and lesions of the mesial temporal region.[1]

Since the demonstration of this important fact, an enormous literature has accumulated regarding the autonomic features of epileptic seizures (*see* references in Marchand and Ajuriaguerra, 1948). This literature, however, has dealt largely with the clinical description of these seizures and little attempt has been made to deal with these attacks as natural experiments in autonomic physiology or to record the multitudinous data which they afford in a graphic manner. While an interesting series of autonomic recordings were made by Jung (1939) in 4 patients suffering from *petit mal* epilepsy, it has not been possible to discover other studies of multiple autonomic function in patients subject to automatism of temporal lobe origin apart from those made under the stress of an attendant operative procedure.

The present study was based upon observations made during 20 seizures in 13 patients subject to epileptic automatism judged to arise from the temporal region. All 20 seizures were of minor degree and no attacks subsequently progressing to a generalized tonic-clonic seizure were included. Post-ictal automatisms or confusional states were also omitted from present consideration.

[1]As Penfield and Jasper (p. 515, 1954) point out, automatism may be seen in association with epilepsy arising from the mid-line region ("centrencephalic discharge") as well as from frontal and temporal areas.

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The graphic recordings of the changing autonomic functions during these little attacks form the data under consideration. From this material, it has been possible to discern some general patterns of autonomic action and some evidence regarding the interdependence of autonomic functions under the conditions imposed by the seizure state.

## METHODS

*Patient material.*—The patient material (*see* Table I) consisted in individuals suffering from epilepsy whose seizures had proved unresponsive to medical treatment and who had been admitted for consideration of excision of their epileptogenic lesions. The period of observation varied from one to eight months. In most instances, the patients were studied when medication had been withdrawn. The recording periods varied in length with the minimum observation intervals of about three hours. In most instances they were started either immediately following breakfast or lunch and continued as long as the patient could cheerfully tolerate the restraint. By these prolonged examination periods it has been possible to collect a number of spontaneous seizures which we thought to be of particular value for the present study. In instances where it was not possible to obtain a spontaneous seizure, activation was attempted by hyperventilation in periods of five minutes or more and by intravenous metrazol administration. Since our aim was to avoid a generalized convulsion it was often found advantageous to administer the metrazol rather slowly, i.e. ½ mg. per kg. of body weight per 30 seconds. If no seizure was encountered after dosage of 10 mg. per kg. of metrazol the injection usually was terminated to avoid an eventual generalized seizure (cf. Ajmone-Marsan and Ralston, p. 159, 1957). It will be noted in the case summaries that most patients were free of any neurological sign of organic damage to the central nervous system. The electroencephalographic data are summarized in Table II.

20 attacks were observed in 13 patients. In all patients at least one attack with complete loss of responsiveness was observed by the present recording methods, but in addition, in instances where attacks with autonomic changes were observed in the same subjects without complete unconsciousness the findings were also included in the analysis. No observations were included which proceeded to a general tonic-clonic seizure. 7 attacks were spontaneous (N. A., N. B., 3 of P. M., E. P., J. B.), 7 induced by metrazol (D. B., W. F., W. B., I. M., E. P., M. R., C. W.) in dosages of 5–12 mg./kg., 3 were induced by hyperventilation (all in J. B.) and 3 by depth stimulation with implanted electrodes (E. S., I. M., G. T.).

*Recording apparatus.*—The recording apparatus was a composite of a number of commercially available recording devices and the author is deeply indebted to Mr. Grant Riggle and Mr. George Johnston[1] for their skill and patience in modifying and assembling the apparatus. The recording instrument was an eight channel ink writing Gilson Medical Electronics Polygraph. This was supplied with one EEG, one EKG, one carrier amplifier, and four multipurpose bridge amplifier channels. The final pen was kept as a time and event marker.

*Blood pressure.*—Direct intra-arterial measurement of blood pressure was initially considered but rejected on several grounds. Any painful or disturbing procedure so profoundly modifies the patient's autonomic responses that any further changes due to epileptic discharge may be exceedingly difficult to evaluate. The possibility of arterial injury due to movement of an inlying needle had to be considered since many of the patients' automatisms included violent motor activity. Lastly, since repeated procedures were contemplated on the same patient, it was considered advisable to

[1]Instrument Section, Laboratory Aids Branch, Division of Research Services, NIH.

TABLE I.—CASE SUMMARY

*Age, Sex, Possible cause*

TABLE I.—CASE SUMMARY

| *Name* | *Age, Sex, Handedness* | *Possible cause of seizures* | *Aura* | *Seizure pattern* | *Post-ictal phenomena* | *Neurological examination* | *X-ray findings* |
|---|---|---|---|---|---|---|---|
| C. W. | 28 y. M R | Unknown | Rising epigastric sensation; feeling of familiarity, hallucination | Automatism, mastication | Aphasia | Negative | Negative |
| D. B. | 44 y. F L | Difficult birth | Floating feeling | Automatism and general fits | ? weakness of right limbs | Smallness of right arm and leg | Dilated L. lateral ventricle |
| E. P. | 30 y. F R | Head injury at 2 yrs. | Face flushes numbness of fingers and toes bilaterally | Automatism, head to left | Mild confusion, sleeps | Negative | Negative |
| E. S. | 26 y. M R | Head injury at 19 yrs. | Ringing sound then auditory hallucination | Automatism with chewing | Brief confusion | Negative | Dilated R. temporal horn |
| G. T. | 24 y. M R | Difficult birth | Dizzy sensation | Automatism, flushing face, tearing, general fits | Confusion | Negative | Negative |
| I. M. | 42 y. F R | Unknown | None | Automatism, grimacing incontinence general fits | Confusion | Negative | Post-op dilated L. temporal horn |
| J. B. | 27 y. M R | Unknown | Epigastric sensation | Automatism, head to right; twitching right face two general fits | None | Negative | Slightly dilated L. lateral ventricle |
| M. R. | 32 y. F R | Family history of seizures | Epigastric sensation; heart pounds; nausea | Automatism, general fits | Confusion | Negative | Negative |
| N. A. | 22 y. F R | Unknown | Tingling in legs; tightness of epigastrium, chest, head | Automatism, head to right, cries out | None | Negative | Mild dilatation parts 2 and 3 of both ventricles |
| N. B. | 32 y. F R | Unknown | Unlocalized feeling of nervousness | Automatism, head to left mouth movement | Aphasia | Negative | Elevated L. petrous ridge |
| P. M. | 36 y. F R | Difficult birth | Coldness R forehead; visual illusions | Automatism grimacing, lip smacking, cries out | None | Negative | Mild dilatation R. temporal horn |
| W. B. | 32 y. M R | Unknown | Difficulty thinking of words | Automatism and general fits | Aphasia | Mild aphasia | Negative |
| W. F. | 32 y. M R | Head injury at 10 yrs. | Sensation of turning | Automatism with violent struggling; lip pursing | Confusion | Negative | Mild general dilatation of lateral ventricles |

TABLE II

| | | RESTING EEG | | | | | EEG DIAGNOSTIC IMPRESSION | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| *Pts.* | *No. of records* | *General background* | *Epileptiform activity and/or focal abnorm.* | *Basal discharges* | *Sleep* | *Metrazol seizure* | *TQ* | *TU* | *TB* | *Extra-temp. involv.* |
| C. W. | 15 | Normal | Temp. | + | − | (4)<br>−L. post. temp.<br>−L. temp.<br>−L. temp.<br>−L. post. temp. | | X | | X |
| D. B. | 3 | Alpha and diff. theta | Temp. mid.-post. | + | − | (1)<br>−R. hemisph. | | | X | |
| E. P. | 6 | Normal (some theta) | Temp. ant.-middle | n.u. | + | (1)<br>−L. hemisph. | | | X | |
| E. S. | 11 | Normal | Temp. posterior and occipit. | O | − | (2)<br>−L. Temp.<br>−occipit.<br>−diffuse | X | | | |
| G. T. | 19 | Normal | Temp. diffuse | + | + | (3)<br>−Bitemporal<br>−diffuse<br>−R. temp. | | | X | |
| I. M. | 17 | Alpha and diff. theta delta | Temp. (?) diffuse | 0 | (?)+ | (2)<br>−L. temp.<br>−L. temp. | | | X | |
| J. B. | 6 | Alpha and diff. theta | Diffuse Mx. R. hemisph. | n.u. | + | (1)<br>−R. hemisph. | X | | | X |
| M. R. | 26 | Alpha and diff. theta | Temp. (?) diffuse | 0 | − | (4)<br>−Max. L.<br>−Max. L.<br>−L. hemisph.<br>−L. hemisph. | | | X? | |
| N. A. | 9 | Normal | Temp. diffuse | ? | + | (2)<br>−Neg.<br>−L. post. temp. | | X | | |
| N. B. | 6 | Diff. theta and delta | Temp. ant.-middle | 0 | + | (1)<br>−L. temp. | | X | | |
| P. M. | 6 | Normal (some theta) | Temp. (?) diffuse | n.u. | − | (2)<br>−Diffuse<br>−Diffuse | X | | | X |
| W. B. | 3 | Alpha and diff. theta | Temp. diffuse | + | − | (1)<br>−L. temp. | | | X | |
| W. F. | 3 | Diff. theta | Temp. ant.-middle | + | − | (1)<br>−Diffuse | | X | | |

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## TITLES FOR TABLES

### TABLE I

A summary of some pertinent clinical details of the present patient material. The patients' initials may be compared with the initials given at the top of each autonomic record (figs. 1–13).

### TABLE II

The number of records taken in each patient does not include the tracings obtained post-operatively (temporal lobe excision) except in a few cases in which polygraphic analysis was carried out following the operation.

The EEG patterns, as outlined, reflect the general impression obtained from an analysis of all the tracings in each given patient.

The EEG diagnostic impression is likewise the result of all the EEG findings both in resting conditions and during various activation procedures.

The type of background activity is also determined by the most constant features: thus, in a given patient, with repetitive findings of a completely normal background, the sporadic (i.e. post-ictal) occurrence of some diffuse slow activity is disregarded and the background will be considered "normal."

"Epileptiform activity" includes any type of random paroxysmal discharges of various form and amplitude. The question mark stands for focal slow abnormalities only, or for very low voltage paroxysmal transients.

Pharyngeal electrodes (for "basal discharges") were not used in 3 cases (n.u.).

A plus sign in case of sleep tracings represents either a real activation (i.e. presence of discharges which were absent in waking conditions) or just a slight increase of pre-existing abnormalities.

The figures in parenthesis in the column of "Metrazol seizure" refers to the number of seizures elicited and recorded in each patient. The topographical distribution of the electrographic changes accompanying each seizure is outlined in the same column.

Separate metrazol activations were used for the EEG and the autonomic studies.

TQ = questional temporal.
TU = unilateral temporal.
TB = bilateral temporal.

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avoid any unpleasant procedure which might interfere with co-operation. For this reason, the Colson Model 110 Automatic Blood Pressure Recorder was selected. This instrument depended upon the coincidence on two consecutive occasions of an auditory and pressure impulse from the brachial artery. As the instrument recorded a pressure, whether diastolic or systolic, a mark was made on the recording line and the actual pressure in mm. of mercury was noted by the operator adjacent to this mark. In instances where it became necessary to attend to other details at the time of registering of the blood pressure, a simultaneous but separate record of the actual blood pressure measurements was made by the machine from which the pressures could be subsequently obtained. In practice the apparatus proved as accurate as manual recording of blood pressure and subject to the same difficulties. It was necessary that the subjects remain moderately still with the arm extended in order to obtain an accurate reading. In a few individuals with firm subcutaneous adipose tissue and a faint brachial artery sound, accurate recording of blood pressure both by the machine and the usual method was not possible.

Errors in recording of blood pressure could be introduced in two ways. Since the pressures in the cuff were recorded when two successive simultaneous pressure and microphonic impulses from the artery were received by the apparatus, a false reading

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could be achieved by moving the arm or tapping the cuff. In many instances the apparatus would simply give no reading under these conditions. However, in view of this feature, no recordings were accepted unless the subject was quiet. The state of the subject was later confirmed from the photographic record. Recording in this fashion also appeared to assure us that any acceptable pressure recordings were the result of some central process and not simply the vascular adjustment to increased bodily activity. The second error in blood pressure might arise from displacement of the microphone overlying the brachial artery and result in erroneously low recordings. Although the microphone was held firmly in place with adhesive tape, movement, such as pronation of the hand, might cause the relationship of the microphone to the artery to change. In this event the characteristic change consisted in an elevation of the diastolic and depression of the systolic records and the defect was corrected.

*Skin temperature.*—The examination room was air conditioned with a mean temperature of 24° ± 1° C. and a humidity of 35–40 per cent. During the course of several hours recording the room temperature might rise 0·5° C. Skin temperature was recorded by a loop thermocouple placed about the plantar aspect of the right or left great toe and a temperature indicator type T. E. 3 of the Elektrolaboratoriet Electromedical Instruments of Copenhagen. The instrument has the advantage of not requiring an external reference thermocouple. It was checked against an accurate mercury thermometer prior to each observation. This precaution, however, appeared unnecessary as the apparatus did not seem to vary. Observations could be made to 1/10° C.

*Skin resistance.*—Skin resistance was measured by a Fels Dermohm-meter, Model 22A of the Yellow Springs Instrument Company. A constant direct current of 70 microamperes was supplied to the patient and formed the basis for resistance measurement. The resistance was measured between the plantar aspects of the two feet.

The electrode paste was found to be of importance as the use of paste especially designed to reduce skin resistance (such as a paste commercially available for EKG use) gave very low resistance in which the usual responses were muted. The most satisfactory electrode paste consisted of 6 grammes zinc sulphate, 60 grammes of bacto agar mixed with 534 c.c. of distilled water, warmed over a water bath until nearly but not quite jelled and then allowed to cool. In the following records, a full pen deflection on the skin resistance line usually corresponded to 10,000 ohms. The instrument automatically re-set itself for every 10,000 ohms change whether in an upward or downward direction and this may be seen on the record as the rapid nearly vertical movements of the pen. In a few individuals with an exceedingly responsive skin resistance, it was necessary to increase the cycling interval to 50,000 ohms to prevent undue disturbance of the record. In any case, the actual resistances were included for reference. Due to an external shunt provided by other apparatus in contact with the patient the skin resistance recorded is about one-half that found when all electrical contacts were removed.

*EKG.*—The electrocardiogram was recorded in the usual way between the right arm and left leg. The ground in most instances was applied to the right leg.

*Pressure recording.*—One of the pressure channels was supplied by a Statham Pressure Transducer Model P23AA which was fed into the carrier amplifier of the Gilson Polygraph. With proper amplification, it was found possible to easily record pressure gradients in the region of 1 mm. of water. This channel was used either for measurement of æsophageal pressures as indicated below or for measurement of the finger plethysmogram.

The latter recording device consisted of a 2·5 cm. glass tube supplied with a rubber

cuff at one end through which the finger was thrust and which prevented air escape about the finger. The other end of the tubing was attached by a short length of heavy rubber tubing to the pressure transducer. Due to the fact that this apparatus was often the first to be displaced during an automatism, the usual aqueous medium was replaced by air so that the apparatus could be reapplied with the least delay when the subject became tractable after the seizure.

The record was subject to numerous movement artefacts and the actual outline of the pulse waves could be modified by external variants and lack of an aqueous conducting medium. Thus, the only observations considered were variations in the amplitude of the pulse wave. A decrease in amplitude was only accepted if the baseline remained relatively steady indicating that significant finger movement had not occurred. This was important since, for example, partial withdrawal of the finger might increase the pressure of the occluding rubber cuff on the finger and hence result in a decrease in the amplitude of the pulse deflection.

The remaining three pressure channels were dependent upon differential pressure meters, Model 303–2, supplied by the Decker Aviation Corporation. This instrument was modified to measure up to 40 cm. of water pressure and had the advantage in that the pressures in cm. of water could be read directly from a dial set in the face of the instrument.

Œsophageal and intragastric pressures were measured by means of a double lumen tube constructed of 2 lengths of polyethylene tubing approximately 1·5 mm. in diameter tied together at convenient intervals. These tubes terminated in balloons made of condom rubber which were about 6 cm. in length. It was customary to maintain a baseline pressure of about 10 cm. of water in the balloon placed in the stomach. The tolerance of the baseline pressure within the œsophagus varied considerably from patient to patient. Some individuals found that the pressure was intolerable and precipitated repeated swallowing and gagging. In most instances, however, a baseline pressure of 2–4 cm. of water could be maintained which was adequate to record the æsophageal peristalsis. Due to this variable tolerance to œsophageal distension, the accuracy of recording of the œsophageal movement was not uniform.

In view of the work of Penfield and Faulk (1955) the use of the electrogastrograph was considered but it appears to present an exceedingly complicated record, being a composite of gastric motor and secretory activity and dependent upon such variables as the composition of gastric juice, mechanical movement of the intragastric electrode and changes in peripheral skin resistance to mention but a few (cf. Martin and Morton, 1952).

Respiration was recorded by the usual laboratory rubber accordion type pneumograph connected to one of the pressure channels. In the initial observations, pneumographs were placed both high over the chest at the level of the axillæ and over the epigastric region. In later examinations, where one of the channels was used for plethysmographic recording, a single pneumograph was used which was placed over the epigastrium. Placement of the pneumograph here served two purposes. Respiratory movements were recorded and the trace also served to record chance movements of the abdominal musculature which might otherwise have interfered with interpretation of intragastric pressure variations.

*Time marker.*—Initial difficulty was seen with the paper drive mechanism and this may be noted in some of the records. The time marker activated by a synchronous motor served as a check upon the accuracy of the paper drive and provided a baseline from which the cardiac frequency could be calculated with confidence. In the tracings the cardiac frequency was indicated by counting over a ten-second interval. Because of the rapid nature of the changes a short interval for the rate count was

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deemed necessary but obviously a difference of 6 beats or so a minute from one reading to another was not considered within a significant range.

*Stimulation.*—Because of their severe incapacity and the unresolvable nature of the clinical and electrographic findings, depth electrodes were inserted in the temporal region in 3 patients (E. S., G. T., I. M.) in an attempt to better our evidence of the localization of the epileptic process (cf. Ajmone-Marsan and Van Buren, 1957). Stimulation in depth in these cases was carried out through needles of stainless steel insulated except for their tips. 4 contacts at 10 mm. intervals were provided and stimulation was carried out between two adjacent contacts. A Grass square wave generator was used for stimulation usually employing 2·5 ms. pulses at a frequency of 60 cycles per second. The current flow usually varied during the stimulation so that the milliamperages recorded are approximate averages. The current was not intentionally allowed to exceed 2 milliamperes at any time (cf. Bickford *et al.*, 1953). The localizations of the electrodes are given in fig. 13 (*see* Plates at end of article).

## Results

### *A. Consideration of Individual Functions*

(1) *Level of consciousness.*—It may be well to define rather precisely the type of attack we have included under the term "automatism" and how one was recognized when in progress. All patients included in this study, in their inter-ictal state, were alert and anxious to co-operate to the point of enduring the minor discomforts and prolonged immobility required by the observation situation. They were under strict orders to avoid movement and verbal communication, except for giving warning of an impending attack or other information specifically requested by the observer. If the subject broke these rules he was gently rebuked and questioned and if inaccessible to sharp command was judged to be in an automatism. This state, however, was not distinctly defined and several patients (N. A., I. M., P. M., M. R., J. B.) acknowledged the observer's command by a glance or a simple word or syllable yet persisted in the act which had been forbidden. In like manner, memory might be partially retained. For example, J. B. recalled the photographic flash being discharged "two or three times" whereas in all 7 flash pictures had been taken before he obeyed the observer and lay quietly once more. C. A. on another occasion, recalled a few of the nonsense words repeated by the examiner during a period when he was unresponsive.

Although in many instances the patient was unresponsive during apnœa, one striking exception occurred. I. M. (fig. 10) responded to depth stimulation by expiratory apnœa. As soon as this was noted on the trace she was questioned and her reply is recorded. After her seizure, she had no memory of this.

(2) *Blood pressure.*—A definite hypertension with rise of both systolic and diastolic pressures was commonly but not invariably seen in periods of automatism (11 out of 20 observations) (figs. 4, 6, 10, 11, 12, 13). No evidence of a fall in blood pressure was seen at any time. In many cases important changes were probably eliminated due to movement artefact.

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Since the record was repeated at only 60 second intervals, changes of short duration may well have been overlooked.

(3) *Surface temperature* (*plantar aspect of great toe*).—A curious finding was that the occasional subject would exhibit a digital temperature as much as 2° C. below the environmental temperature (D. B.). A fall to this temperature was never observed during any recording period so it presumably reflected the environmental temperature to which the subject had previously been exposed. However, this low temperature might persist for an hour or more in the examination room.

Hyperventilation occasionally produced a fall in digital temperature (J. B., W.B.). During sleep or following a seizure digital temperatures as high as 36° C. have been recorded.

The skin temperature was found to vary following automatisms. In the immediate post-ictal period the digital temperature was seen to rise (figs. 3, 6). In fig. 3 the rise was particularly steep and transient reaching a maximum six minutes following the attack and declining thereafter. The temperature was twice seen to fall in the post-ictal period. The rise or fall of the post-ictal surface temperature did not appear to be related to the surface temperature just prior to the seizure since in the first group the initial temperatures were 24·5, 26·3 and 35·2° C. respectively, while in the latter group the respective temperatures were 24·4 and 32·1° C. The degree of motor activity during the automatism did not seem of importance either since, for example, W. B. required no restraint while W. F. struggled violently for twelve minutes requiring the efforts of 3 attendants to hold him on the bed.

(4) *Pulse-rate*.—Bursts of tachycardia were frequently seen early in periods of automatism. The rapidity of onset and offset of the tachycardia was often surprising (cf. figs. 1, 3). As proved by the photographic record, this paroxysmal tachycardia was not necessarily related to somatic movement. Repeated bursts of tachycardia might appear throughout the course of the automatism (I. M., fig. 8; N. B., fig. 3, W. F.). Only one example of definite bradycardia was seen (N. B., fig. 3).

(5) *Skin resistance*.—The skin resistance demonstrated several characteristics under the test situation which merit consideration.

The usual pattern of skin resistance during an examination ran as follows. The subject would start with a resistance of about 25,000 to 50,000 ohms which would rise another 25,000 to 50,000 ohms as he became habituated to the observation conditions. With phlegmatic individuals (e.g. G. T., and J. B.) the initial resistance was higher and the subsequent climb in resistance less. In all cases a period, usually amounting to about an hour, was allowed for stabilization of the record prior to any attempts at seizure induction if this were planned. Sleep accompanied by a further rise in skin resistance frequently occurred

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apparently resulting from the enforced immobility and the steady ticking of the time marker. Awakening was usually signalled by a rapid drop in skin resistance which often had risen to 125,000 to 200,000 ohms. Some individuals might require some additional alerting procedure such as mental arithmetic before the skin resistance would drop to the pre-sleep level (e.g. N. A., J. B.).

Most subjects showed a readily observable fall in skin resistance with deep inspiration on command or in response to simple commands of other kinds (e.g. close the eyes or swallow) (cf. E. P., fig. 2, and W. B.). This was absent, however, in some (e.g. J. B.) though a later record in this patient showed some feeble responses. The skin resistance fall associated with various test situations tended to steadily diminish in amplitude with repetition of the same stimulus at short intervals. A similar experience is reported by Jung (1939). In our work, it was noted, however, that, if a sufficient interval passed during which the patient was otherwise occupied and not under stress, the potency of the stimulus to produce autonomic changes was frequently regained.

Unfortunately, procedures used to precipitate seizures, apart from sleep, usually resulted in a low skin resistance long before the overt seizure occurred so that further ictal skin resistance changes might be minimal or absent. Hyperventilation lowered the skin resistance (J. B., W. B., P. M.). Simple venepuncture itself might depress the skin resistance for over an hour. With very few exceptions (e.g. E. P., fig. 7) metrazol even in small dosage reduced the skin resistance to near minimal levels.

Despite this fact some pre-ictal fall of skin resistance was a common finding occurring in 18 of the 20 observations. A well-defined response might amount to a fall of 15,000 to 50,000 ohms and was usually rapid (fall occurring in 10–20 seconds). No sudden or marked rises of skin resistance were noted, although *during* the automatism a slight rise was noted twice (W. B. and C. W.). It is to be noted that during the metrazol administration the skin resistance in both cases had reached a very low figure for the individual.

During recovery from a seizure the skin resistance rose slowly. The recovery rate of 10,000 ohms per one to two minutes (N. A., fig. 1) was of distinctly unusual rapidity. This slow rate of recovery was, in general, similar to that seen when the skin resistance was reduced by other measures.

(6) *Finger plethysmogram.*—Measures resulting in a fall of skin resistance were often associated with a narrowing of the plethysmographic record. This was best demonstrated by W. B., whose skin resistance and plethysmogram were unusually sensitive to external stimuli.

When a change in the plethysmogram appeared, it was seen early in the pre-ictal phase as a gradual narrowing of the amplitude of the pulse wave (J. B., N. B., fig. 3). Due to the invariable displacement of the apparatus

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or movement associated with the automatism no records of the recovery phase were judged worthy of evaluation.

(7) *Œsophageal motility.*—Since the balloon was placed in the lower half of the œsophagus the involuntary nature of the contractions in this area was frequently seen and their variable dependence upon the laryngeal phase of deglutition reaffirmed (cf. Cannon, p. 260, 1915; Babkin and Van Buren, 1951). In some instances, at least it appeared that the presence or absence of an adequate saliva bolus was an important factor in determining the presence or absence of a propagated œsophageal peristaltic wave.

Although the laryngeal movements of swallowing and/or œsophageal peristalsis were seen in the pre- and/or post-ictal periods of 13 of 20 automatisms these were encountered but twice (G. T., fig. 13, and E. P., fig. 7) during the unresponsive period in this small series.

(8) *Gastric motility.*—The peristaltic contraction pattern of the human stomach was found to consist in forceful (usually over 40 cm. water pressure) contractions which started slowly with a steady rise in the velocity of application of the pressure toward their peak followed by a fall of pressure, initially rapid, which subsequently slowed as the baseline was approached. A complete contraction lasted 20–30 seconds and tended to recur at 1–2 minute intervals. The rhythm of the contractions might be irregular. This frequency was slower than the dog (Babkin and Van Buren, 1951) and corresponds with the frequency of the human hunger contraction (Cannon and Washburn, 1912, and Carlson, 1914) though the contractions recorded in the present study caused no sensation. We have not observed the 10–12/minute contractions reported by some workers other than the respiratory artefact which may be superimposed upon the gastric tracing. Periods of gastric peristalsis tended to come and go without obvious cause or symptoms. Whether or not the meal immediately preceding the record was eaten or withheld did not seem to significantly alter our chances of finding a regular pattern of peristalsis.

One example of duodenal peristalsis was observed (quite fortuitously) in the present study. The frequency of these waves was considerably higher, approaching the respiratory frequency but being quite distinct from this movement (fig. 5) and the force of the contractions was less than that of the gastric activity.

Inhibition of gastric contractions was seen to accompany deepening sleep in N. A. and hyperventilation in S. B., P. M., J. B., and D. B.[1] Metrazol administration caused the cessation of gastric peristalsis in all instances; even the prospect of receiving the drug seemed an adequate inhibitory stimulus in one case at least.

Thus, well-developed gastric peristalsis was present at the start of only

[1]Hypocapnia is known to inhibit gastric secretion induced by vagal stimulation (Babkin, p. 849, 1949).

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2 spontaneous automatisms (N. A., fig. 1 and P. M., fig. 4) and the contractions were inhibited in both. The apparent post-ictical motor effect noted in E. P. (fig. 7) seemed due to the patient pulling the balloon into the lower œsophagus during her automatic period. The sudden collapse of peristalsis at the end of the record was considered the result of the balloon suddenly re-entering the more capacious gastric lumen. No effect upon the duodenal motility was noted during a minor automatism in P. M. (fig. 6). One feeble post-ictal contraction of questionable validity was seen in I. M. (fig. 8) following seizure induction by metrazol. A paradoxical effect was observed by depth stimulation in E. S. (fig. 11). At the start, depth stimulation in the right pes hippocampus (cf. localization in fig. 9) brought about the cessation of pre-existing regular gastric peristalsis. Something over an hour later, repetition of the stimulus to the same area produced transient gastric motor activity, along with loss of responsiveness and other autonomic phenomena. No peristalsis had been present during the hour separating the two stimuli.

In view of Hoffman and Rasmussen's (1953) work, the records were reviewed for changes in baseline gastric tonus but no convincing alterations were seen. Those that appeared were associated with changes in the tracing of the pneumograph placed over the epigastrium (to monitor movements of the abdominal walls) and so were discarded.

It was not possible satisfactorily to relate the pre-ictal epigastric aura to gastric motor phenomena since only one such observation was made (C. W.). In this case, in which peristalsis was absent, there was no change in the record of intragastric pressure during the epigastric aura. One point of possible interest was that P. M. noted a definite non-painful epigastric sensation as the inflated gastric balloon passed into the duodenum (fig. 5), and, curiously enough, reported it was much like an occasional pre-ictal sensation in this location.

(9) *Respiration.*—Respiratory changes were the commonest phenomena during automatisms being present in some degree in all attacks and striking changes might be repeated in the same attack (this accounts for the number of respiratory changes in Table III exceeding the number of observed attacks).

Apnœa was most frequently seen and, when present, the chest assumed an expiratory position in all instances. Less frequently respiration was inhibited (decrease of respiratory frequency with or without a decrease of respiratory amplitude). Irregularity of respiratory frequency alone or tachypnœa were infrequent and the latter was never well marked (cf. W. F.).

Initially, pneumographic records were made over both chest and epigastrium on the possibility that dissociation of the respiratory movements might occur. No certain instance of this appeared.

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TABLE III.—APPROXIMATE SEQUENCE OF APPEARANCE OF PHENOMENA IN 20 MINOR TEMPORAL SEIZURES

| Function | 1st | 2nd | 3rd | 4th | 5th | Totals |
|---|---|---|---|---|---|---|
| Respiratory change | 9 | 6 | 4 | 2 | 2 | 23 |
| exp. apnœa | — 3 | — 2 | — 3 | — 2 | — 2 | —12 |
| inhibit. resp. | — 5 | — 1 | — 1 | | | — 7 |
| irreg. resp. | — 1 | — 1 | | | | — 2 |
| irreg. tachypnœa | | — 2 | | | | — 2 |
| Tachycardia | 2 | 7 | 4 | 6 | | 19 |
| Fall S.R. | 11 | 4 | 2 | 1 | | 18 |
| Rise B.P. | | 5 | 4 | | 2 | 11 |
| Swallow | 6 | 4 | 3 | | | 13 |
| Unresponsive | 1 | 4 | 6 | 2 | 1 | 14 |
| Auræ | | 8 | 2 | 1 | | 11 |
| cephalic | | — 2 | | | | — 2 |
| body | | — 2 | | — 1 | | — 3 |
| chest | | — 1 | | | | — 1 |
| epigastric | | — 1 | | | | — 1 |
| cold | | — 1 | — 1 | | | — 2* |
| movement | | — 1 | | | | — 1 |
| desire to void | | | — 1 | | | — 1 |
| Flush face | | | | 1 | 1 | 2 |
| Resisting (active) | | 2 | | 1 | 1 | 4 |
| Rise S.R. | | 1† | | 1† | | 2 |
| Bradycardia | | 1 | | | | 1 |
| Retching | | 1 | | | | 1 |
| Cough | | | 2* | 1* | | 3* |
| Phonation | | | 1 | | | 1 |
| Void | | | 1 | 1 | | 2 |
| Loss gastric peristalsis | | | 1 | 1 | | 2 |
| Tonic posturing | | | | 1 | | 1 |
| Twitching eyelid | | | | 1* | 1* | 2* |
| Lacrimation | | | | | 1 | 1 |

*All in same individual. †S.R. fall very low early in metrazol activation.



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TABLE III

A summary of the approximate temporal sequence of various clinical and autonomic phenomena attending minor epileptic seizures in patients suffering from seizures of temporal origin. The sequence is indicated from first to fifth events. Approximately simultaneous events are placed together in the same box. Later recurrence of the same event (e.g. paroxysmal tachycardia) is also indicated in its proper sequence. See text for further discussion.

### *B. Integration of the Autonomic Recordings, Their Temporal Relationships and Correlation with Patient Responsiveness*

In summarizing the previous section, the positive findings usually associated with automatism consisted in hypertension, paroxysmal bouts of tachycardia, precipitous falls in skin resistance, narrowing of the pulse wave of the finger plethysmogram, occasional pre-ictal swallowing inhibition of gastric peristalsis and interference with respiration usually consisting in expiratory apnœa, or slowing of the respiratory rate. Post-ictal changes tended in a direction to restore these functions to their control level with the exception of the digital surface temperature which usually rose for several minutes.

Close comparison of the temporal relationships of the various autonomic phenomena would have been an easy matter if all were continuous functions such as the skin resistance. This was not the case, however, since most functions were cyclic or intermittent in character with frequencies varying from *c.* 75/min. for the heart rate to *c.* 1 contraction every 1–2 minutes for the gastric peristaltic rate. An artificial cycling time was introduced in blood pressure recording. Thus, Table III was drawn up with some hesitancy since changes had to be considered synchronous with others when they occurred "about" the same time or were separated from others when they "seemed" to precede or follow, by a matter of several seconds. Despite its shortcomings, the table suggests certain trends which merit consideration but should not be taken too literally.

As to the general pattern of an automatism, the initial features usually consisted in a fall of skin resistance and swallowing. Respiratory changes might appear as initial phenomena but variations in this function might appear at any point in the attack. Changes in pulse frequency (tachycardia) tended to appear somewhat later and were often accompanied by hypertension. At about the same time the majority of the auræ associated with the attack were reported. Unresponsiveness followed.

This tendency for autonomic change to precede the clinical automatism was strikingly exemplified in G. T. in whom with depth stimulation it appeared possible to fractionate the attack by current variations. Thus the sequence induced by currents of increasing strength and duration roughly paralleled the general sequence seen in Table III. The weakest stimulation (fig. 12) resulted most obviously in inhibition of respiration

followed by tachycardia and swallowing. A somewhat greater stimulation added hypertension to this sequence (fig. 12 B). With the final stimulation a fully developed automatism was produced which was typical of his usual spontaneous seizures (fig. 13).

Although this general sequence was evident, it was equally apparent that almost any of the autonomic changes might present as the initial phenomenon. It was of interest, too, that changes in autonomic function usually *preceded* the report of an aura or the appearance of unresponsiveness.

Some examples of the pattern differences may be cited. In both the spontaneous and metrazol attacks of E. P. (figs 2 and 7) unresponsiveness appeared much earlier in relation to the autonomic features than in any of the other subjects. The spontaneous attack of N. B. (fig. 3) showed irregularity and slowing of respiration prior to the pulse changes (first tachycardia then bradycardia) which were well before the skin resistance fall. N. A. showed skin resistance fall and a striking tachycardia shortly followed (fig. 1).

When repeated attacks were seen in the same individual the sequence might vary to some extent or remain stable. In all 4 attacks observed in J. B. fall of skin resistance was an intial feature though combined with swallowing in 2 attacks and expiratory apnœa in a third. The 3 attacks of P. M. appeared of lesser clinical severity; in one, autonomic changes accompanied sensation of movement without evident alteration of consciousness. In 2 of the 3 attacks skin resistance fall with respiratory changes of inhibitory character were seen early while in the last attack swallowing, rise of blood pressure and expiratory apnœa preceded the fall in skin resistance. One of the attacks (fig. 4) exhibited a curious biphasic character not seen in any of the others; the initial skin resistance fall was followed by transient recovery only to fall again later in the attack.

## Discussion

### (1) *Comparison of the Present Results with Previous Graphic Recordings of Ictal Autonomic Phenomena and the Possible Localizing Significance of these Changes in Primates*[1]

There is, unfortunately, not a wide background for comparison with present results. Perhaps the initial human observation was made by Hans Berger (fig. 5, 1934), who recorded the relationship of consciousness, respiratory function and cerebral activity in a woman suffering from "Genuine Epilepsie." His tracing shows a roughly simultaneous onset of unresponsiveness, apnœa and flattening of the EEG which shortly preceded a fully developed seizure. The changes associated with *petit mal*

[1]Due to the difficulty in homologizing the cortical areas in carnivores and man, only evidence from primates and man is included in the present summary. An extensive bibliography on the subject may be obtained from Kaada (1951).

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attacks (2–3/sec. wave and spike) were observed by means of multiple autonomic recording by Jung (1939). In this study he illustrates respiratory inhibition (or apnœa), fall in the amplitude of the plethysmographic pulsations and skin resistance changes. No particular changes were noted in the EKG. The tendency for association of the fall in skin resistance and the narrowing of the plethysmographic record was also noted and considered a part of sympathetic excitation. Fischgold and Arfel-Capdevielle (1955) studied respiratory changes both with *petit mal* seizures and those considered of temporal origin. Inhibition of respiration or arrest in expiration occurred in both types of seizures but the alterations in consciousness were more likely to accompany the expiratory arrest with *petit mal* than with the 4 instances of temporal seizures which they report. Although the relationship is admittedly variable, we not infrequently observed unresponsiveness with respiratory inhibition in temporal automatism and a similar relationship was found by Kaada (1951), Liberson *et al.* (1951) and Scoville (1954) on mesial temporal stimulation in man. Mosier *et al.* (1957) observed general seizures induced by metrazol in which the skeletal motor components had been eliminated by succinyl choline. Hypertension and tachycardia were common but 9 of 41 patients exhibited cardiac arrythmias of various types (auricular and ventricular premature contractions, short runs of bigeminy, ventricular tachycardia and short runs of bidirectional ventricular tachycardia). The arrythmias were usually seen with the clonic phase of the attack. Penfield and Jasper (1954) report an instance of gastric motor inhibition during an automatism (A. Ki). The fact, however, that the peristaltic frequency was 6–10 contractions per minute might suggest that the activity was duodenal (or respiratory) rather than gastric.

With regard to the possible localizing significance of the present autonomic phenomena, it is pertinent to review the results of surface stimulation in primates and man and what is available regarding depth stimulation. The subject is ably reviewed in Kaada's (1951) excellent monograph. There he points out an area starting in the anterior cingulate region, extending downwards along the subcallosal gyrus to spread out along the posterior orbital, anterior and mesial temporal surfaces and insula from which the majority of cortical autonomic responses may be obtained in the monkey.

Not all of the responses recorded in the present studies have received consideration in primate cerebral physiology. This is particularly the case with skin resistance, the plethysmogram and œsophageal motility. The available evidence will be summarized under (1) Consciousness; (2) Respiration; (3) Blood pressure; (4) Cardiac rate; (5) Gastric motor function; (6) Surface temperature; (7) Finger plethysmogram, and (8) Skin resistance.

(1) *Consciousness.*—Loss of alertness and reaction to their environment without generalized seizures have been seen in monkeys in seizures produced by alumina

cream applications on the first temporal convolution just below the Rolandic fissure (Huertas and Forster, 1954) and in the amygdala (Sloan *et al.*, 1953).

In human epileptics the areas from which automatism appeared to arise centred on (1) the circuminsular temporal cortex, (2) the amygdaloid nucleus, (3) the anterior temporal gyrus or hippocampus, (4) the termination of the anterior commissure. Curiously, the posterior hippocampal gyrus after removal of the tip of the temporal lobe did not appear concerned with this process (Penfield and Jasper, p. 530, 1954; also Penfield *et al.*, 1952; Penfield, 1955; Forster and Huertas, 1955–56). Stimulation near the uncus (anterior hippocampal gyrus, temporal pole and portions of the temporal pole close to the insula) was found to depress the conscious level in varying degree both in psychotic and epileptic patients (Liberson *et al.*, 1951; Kaada and Jasper, 1952; Scoville, 1954). This is apparently the only area from which consciousness may be altered by cortical stimulation short of stimuli which result in a seizure.

(2) *Respiration.*—Although acceleration of respiration may result from stimulation, superiorly in the precentral region or just anterior to it in primates (Spencer, 1894; Bechterew, p. 1599, 1911; Smith, 1938), the predominant respiratory effect of cortical stimulation is inhibitory in character characteristically taking the form of expiratory apnœa. This has been obtained from the inferior precentral region in monkey and man (Bucy and Case, 1936; Smith, 1938; Walker and Green, 1938; Penfield and Jasper, p. 61, 1954) and from the anterior cingulate region in monkey by Smith (1945), Ward (1948), Kaada *et al.* (1949), and in man by Pool and Ransohoff (1949) and Penfield and Jasper (p. 108, 1954).

A similar inhibitory response has also been obtained in monkey from the subcallosal, posterior orbital, anterior insular, anterior hippocampal gyrus and temporal polar regions by Kaada *et al.* (1949) and the various observations are confirmed by Smith (1938), Bailey and Sweet (1940), Delgado and Livingston (1948), Sugar *et al.* (1948), Sachs *et al.* (1949). This response has been confirmed by stimulation of analogous areas, i.e. posterior frontal, mesial temporal and anterior insula, in man (Livingston *et al.*, 1948; Chapman *et al.*, 1949; Chapman *et al.*, 1950; Liberson *et al.*, 1951; Kaada, 1951; Kaada and Jasper, 1952; Glusman *et al.*, 1953; Penfield and Jasper, 1954).

In man, under general anæsthesia, respiratory inhibition or apnœa has been obtained from the region of the nucleus ventralis anterior thalami, anterior hypothalamus, and red nucleus (Dell and Talairach, 1954). In lower primates respiratory arrest was found to follow stimulation of the head of the caudate nucleus (Wall and Davis, 1951).

(3) *Blood pressure.*—In anæsthetized monkeys, blood pressure variations were seen to result from stimulation of the posterior orbital surface (Bailey and Sweet, 1940; Delgado and Livingston, 1948; Sachs *et al.*, 1949); and Kaada, 1951). Wall and Davis (1951) found the responsive area to be nearly coextensive with the area giving maximal respiratory effects as cited above. The direction of the response, although usually consisting in a slow rise in pressure appeared dependent to a considerable degree upon the nature of the stimulus and the anæsthesia. The blood pressure responses were not abolished by destruction of the paraventricular nuclei of the hypothalamus, of the adrenals or section of the vagi and splanchnic nerves (Sachs *et al.*, 1949). However, with what may be a greater area of hypothalamic destruction, Wall and Davis (1951) could abolish the pressor effects from mesial temporal stimulation.

In man, under anæsthesia, stimulation of the orbital, anterior temporal and anterior cingulate regions usually resulted in a pressor response (Livingston *et al.*, 1948; Chapman *et al.*, 1949; Pool and Ransohoff, 1949; Chapman *et al.*, 1950).

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(4) *Cardiac-rate.*—In monkey bradycardia was reported by Smith (1944, 1948) from stimulation of the anterior portion of the hippocampal gyrus and the response could be abolished by vagotomy. Kaada (1951) observed the same response from stimulation of the rostral portions respectively of the piriform and anterior limbic (cingulate) cortex in monkey. Both he and Smith (1945) noted that the relationship of cardiac rate to blood pressure was variable.

Although tachycardia was found on stimulation of the human supplementary motor area in man (Penfield and Rasmussen, p. 78, 1950) both accelerator and decelerator responses were elicited from the human anterior cingulate gyrus (Pool and Ransohoff, 1949). No changes in pulse were seen to accompany changes in respiration and blood pressure evoked from the human posterior orbital region (Livingston *et al.*, 1948; Chapman *et al.*, 1949). Changes in pulse-rate were apparently an infrequent concomitant of stimulation of the insula in man (Penfield and Rasmussen, p. 85, 1950).

In man, White (1940) obtained mild bradycardia from stimulation of the ventricular aspect of the preoptic area. More recently, Dell and Talairach (1954) failed to observe any pulse changes from stimulation of subcortical areas providing well-marked respiratory changes (ventralis anterior thalami, anterior hypothalamus, red nucleus, gyrus cinguli).

The frequent finding of tachycardia in the present study contrasts strongly with the results of local stimulation cited above.

(5) *Gastric peristalsis.*—In monkey Sheehan (1934) noted inhibition of the contractions of the fundus from stimulation of the premotor and frontal areas. A fall in tonus of the gastric fundus was observed on stimulation of the posterior orbital region, insular area, and temporal pole (Bailey and Sweet, 1940; Hoffman and Rasmussen, 1953). The latter authors could abolish the change by vagal section. Both Kaada (1951) and Hoffman and Rasmussen (1953) demonstrated inhibition of established gastric peristalsis in monkey by stimulation of the insula, posterior orbital and mesial temporal regions. Kaada (1951) pointed out that although the fields from which changes in respiration, blood pressure and gastric peristalsis might be elicited overlap, those influencing pyloric motility were more restricted than the others. He also found occasional augmentation of motility from stimulation of the posterior orbital, insular, hippocampal and temporal zones but never from the anterior cingulate region. This effect was most prone to occur if the baseline peristalsis was weak. Inhibition of peristalsis might be obtained without evident alteration of respiration and blood pressure.

Apparently the only human observations are those of Penfield and Faulk (1955). On stimulation of the inferior portion of the insula as exposed by temporal lobectomy they observed inhibition of gastric motility and tone as well as initiation of rapid (10–12/min.) contractions. In the present and another study of human autonomic function, we have not observed contractions of this rapidity in the human stomach.

(6) *Surface temperature.*—In 1948 Delgado and Livingston observed that, in addition to changes in respiration and blood pressure, stimulation of the posterior orbital region in the monkey could induce a rapid rise of temperature in both extremities which could attain an elevation of 6–8° F. Curiously, ablation of the area produced a rise in temperature of the extremity and a less pronounced and prolonged reaction to cold exposure. Since the stimuli resulted in apnœa, the rapid bilateral warming might have resulted from peripheral vasodilatation secondary to a rise in the carbon dioxide tension in the blood. Peripheral warming of a few degrees centigrade can be induced by repeated voluntary breath holding in man (present observations).

Comparable observations have apparently not been made in man, although

Penfield and Jasper (1954, p. 416) do report cutaneous flushing (and presumably rise of local temperature) of the face and neck on stimulation close to the infundibulum.

(7) *Finger plethysmogram.*—Bolton *et al.* (1936*a*) noted vasoconstriction (fall of finger volume)—a concomitant narrowing of the pulse amplitude may also be seen—with deep inspiration much as has been observed in our material (cf. W. B.). In a subsequent report (Bolton *et al.*, 1936*b*) they illustrate a fall in amplitude of the digital pulse wave with hyperventilation as well as a biphasic response—vasoconstriction, then vasodilatation—to a rise in the carbon dioxide tension. All these responses were found dependent upon the integrity of the sympathetic supply to the digit from which the observations were made.

Unfortunately, there appear to be no studies of the responses of the plethysmogram to cortical stimulation.

The post-ictal increase in amplitude of the digital pulse wave, which was seen in a few instances (cf. N. B., fig. 3) would seem more likely due to some type of prolonged sympathetic inhibition (e.g. post-ictal sleep) than to a carbon dioxide effect. The absence of hyperpnœa and the long duration of the response would appear to confirm this view.

(8) *Skin resistance.*—Although no references to changes in skin resistance due to stimulation of the primate brain could be found, some fundamentals deserve mention. Both in monkey and man Richter (1927, 1929) and Richter and Woodruff (1941) pointed out that changes in sweat secretion are responsible for the changes in palmar skin resistance. They demonstrated further that these changes are abolished by interruption of the sympathetic nerve supply. Certain phenomena (Richter, 1929) suggest there may be a small parasympathetic component in these changes antagonistic to the sympathetic activity.

In the cat Langworthy and Richter (1930) noted changes in the galvanic skin response from stimulation of the posterior gyrus proreus and the sigmoid gyrus just beyond the lateral extension of the cruciate sulcus. This confirmed the early work of Bechterew (1911, p. 1730). By stimulation of successive cut brain surfaces, they were able to find the responses in areas of the frontopontine and temporopontine tracts in the cerebral peduncles. Further, posteriorly responses were obtained from the region of the rubrospinal tract and the pyramids. Responses were also obtained by stimulation of the prominences of the vestibular nuclei in the fourth ventricle, the cunate nuclei and the posterior columns of the spinal cord.

In general, it may be seen that the changes observed during the automatisms of temporal lobe epilepsy closely reproduce the alterations in function which result from stimulation of the insula, medial temporal region, posterior orbital, subcallosal and anterior cingulate areas in primates. The pulse-rate, however, stands out against this pattern of conformity. At present there is no satisfactory explanation of this incongruity.

(2) *General Principles of Function Noted in the Present Observations*

(*a*) *The importance of the initial level of autonomic function.*—Although this aspect, which is of importance in determining the direction of an autonomic response, has been well recognized by some workers, it has been neglected in the evaluation of more recent studies and bears re-emphasis (cf. Darrow, 1943).

The importance of the initial level of autonomic function was perhaps best seen in the skin resistance. Thus the susceptibility to change in

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either a positive or negative direction was about equal at the mid-point of an individual's range of skin resistance. As the skin resistance approached the upper or lower limits for that individual, the possible amplitudes of change in a respectively upward or downward direction were progressively damped. The usual effect of a seizure was a rapid skin resistance fall. Under certain circumstances, however (C. W. and W. B.), a mild paradoxical effect could be seen. In both of these instances, the skin resistance had fallen to minimal levels early in the metrazol administration and a rise, rather than fall, was seen during the clinical attack. A paradoxical response was also observed in gastric function (cf. McCrae *et al.*, 1925; Patterson, 1933) (E. S., fig. 11). Stimulation near the tip of the pes hippocampus during regular peristalsis abolished the function. Restimulation of the same point during a period of gastric inactivity set off a transient series of gastric contractions. Both inhibitory and excitatory effects on gastric peristalsis upon stimulation of the human insula have been reported by Penfield and Faulk (1955).

It may be mentioned that evidence of paradoxical changes seemed nearly lacking in cardiovascular and respiratory function. In the case of the pulse-rate it may have been that the nearly universal tendency toward tachycardia was due simply to the fact that the subject was resting quietly with a near basal pulse-rate prior to the seizure. The same, however, certainly did not seem to apply to the respiration since a resting frequency was usually assumed prior to the seizure, yet inhibition of apnœa were by far the commonest effects. One may speculate that autonomic functions also subject to voluntary control (such as respiration) may tend to respond with less regard to their initial level of function than those controlled only by an involuntary mechanism.

(*b*) *The temporal independence of autonomic function.*—On initial consideration of the present data, search was made for patterns of action; patterns of function which might be compared, for example, to the ergotope or trophotrope patterns of Hess (1954). Instead of such patterns a remarkable lack of interdependence of autonomic function came to light. With one possible exception[1] each of the investigated autonomic functions appeared capable of change without affecting the others.

There is precedent for this disintegration of functional pattern in autonomic action. Despite the general patterns cited by Hess, he reported independence of such closely related functions as pulse-rate and blood pressure on hypothalamic stimulation (Hess, p. 19, 1954). Thus, although cardio-accelerator and cardio-inhibitor effects commonly accompany pressor and depressor effects on the blood pressure respectively; this relationship was not absolute. On stimulation of mesial

[1]The skin resistance and finger plethysmogram appeared on occasion to act together; a fall in the former was usually accompanied by a simultaneous narrowing of the amplitude of the pulse wave in the latter.

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temporal structures in anæsthetized monkeys, Kaada (1951) found that disassociation of pulse and blood pressure changes was nearly a rule. Livingston *et al.* (1948) and Chapman *et al.* (1950) pointed out the independence of the hypertensive and apnœic effects of human posterior orbital and temporal stimulation respectively, although the former authors found that the zones from which they might be elicited frequently overlapped. Livingston *et al.* (1948) also noted that these changes were not associated with variations in cardiac rate. From stimulation of the walls of the human third ventricle White (1940) was able to induce pulse variations and changes in blood pressure without affecting respiration. Dissociation of function was also seen with stimulation of the human cingulate region by Pool and Ransohoff (1949).

This evidence of independent autonomic function in no way invalidates the valuable concepts of function in concert under physiological circumstances, but simply points out that, under the artificial conditions imposed by stimulation or seizure discharge, disintegration of the functional nature of the act occurs as is mirrored in the motor sphere, perhaps, by the tonic-clonic fit.

Unfortunately at present there is no serviceable experimental evidence to indicate the significance of these varying temporal patterns of autonomic function. Very few studies of autonomic representation in the central nervous system have been based upon the simultaneous graphic recording of several such functions and, when recorded, the temporal sequence has been invariably disregarded. The fact, however, that disintegration of functional autonomic patterns is possible suggests there is spatial separation of the representation of autonomic function. In the central nervous system this feature is not lacking in importance for if topographical separation of autonomic function exists, there is the possibility that variations in the temporal sequence of autonomic activity may have a practical use in localizing human epileptic discharge.

## Summary

In a group of 13 patients judged by the usual clinical diagnostic measures to be suffering from epilepsy arising in the temporal lobe, a detailed study by graphic recording was made of 20 minor seizures and automatisms. 7 seizures were spontaneous, 7 were induced by metrazol, 3 by hyperventilation, and 3 resulted from depth stimulation with implanted electrodes. Any attacks proceeding to a generalized tonic-clonic seizure were eliminated from present consideration.

The autonomic changes during spontaneous and induced seizures were essentially similar except that during metrazol administration many patients became agitated with accompanying fall of skin resistance, narrowing of the plethysmographic excursion and cessation of gastric peristalsis which seemed unrelated to overt seizure activity. A similar

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effect, although less marked, appeared during hyperventilation or simple venepuncture.

If a change in autonomic function appeared during a minor seizure, its direction of change, in general, appeared quite stereotyped. Thus, the blood pressure rose, pulse-rate increased, skin resistance fell, the amplitude of the deflection of the finger plethysmogram narrowed, swallowing or retching might appear, gastric motility was inhibited and respiration was inhibited usually with the appearance of expiratory apnœa. With the exception of the pulse-rate, the responses thus closely followed those obtained from stimulation of the limbic area in primates. The tachycardia was curious in its rapidity of onset and offset; thus, it might rise from 75 to 130 in a few seconds and slow again nearly as rapidly. Repeated bursts of this type might appear. In the post-ictal period often marked rises in the digital temperature occurred and the other autonomic functions returned to their pre-ictal level.

In the analysis of the data, the importance of the initial level of autonomic function became apparent and appeared to explain some responses which were of paradoxical nature. Thus, in 2 cases in which the skin resistance had been reduced to near minimal levels early in the metrazol administration, a slight rise rather than a further fall was seen during the seizure. In another case, gastric peristalsis was abolished by stimulation near the right pes hippocampus. An hour later, restimulation of the same point by the implanted electrodes resulted in a few minutes of gastric peristalsis although none had appeared in the hour succeeding the first stimulation.

Although search was made for synergistic patterns of autonomic activity, such as the ergotrope or trophotrope patterns of Hess, no such patterns were found. Indeed the various autonomic functions showed a remarkable lack of interdependence in the seizure state.

In charting all the autonomic features of these attacks by their sequence of appearance, a general time sequence might be drawn up. Thus, a fall of skin resistance and/or swallowing tended to appear as the earliest features. Respiratory changes, usually expiratory apnœa, were the commonest of all and might appear early, although this change might appear at any point in the attack. Tachycardia with or without a rise in blood pressure usually appeared somewhat later. Coincident with the cardiovascular changes or even later came the patient's aura or unconsciousness. In only one case did unresponsiveness precede any autonomic change.

Despite these generalities of time sequence the temporal pattern of autonomic and clinical change of an individual attack was far from uniform. This suggested that there was gradual spread of seizure discharge through spatially separated areas of autonomic representation. It

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remains to be seen whether this "march" of autonomic changes may have a practical value as an aid to localization of epileptic seizure discharge.

The author is deeply indebted to Dr. C. Ajmone-Marsan, Branch of Electroencephalography, for his interest and criticism, for preparing Table II in the text and for reviewing the available evidence for possible autonomic-EEG correlations. Dr. Maitland Baldwin kindly permitted the author to include in this study patients admitted to his service. Much of the value of the material was contributed by various observers, namely, Miss K. Eastman, Miss M. Benson, Mr. P. McGrath, Dr. J. Mateos, Dr. G. Long and Dr. R. Edgar who assisted from time to time.

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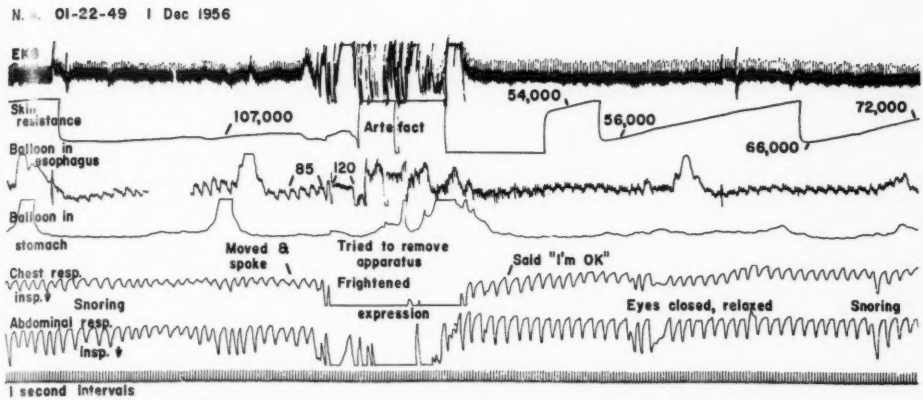


FIG. 1.—Spontaneous seizure observed during sleep. The gastric peristalsis had been regular prior to the seizure and was resumed within a minute following the close of the present record. The paroxysmal tachycardia was indicated by the cardiac impulses superimposed upon the œsophageal tracing.

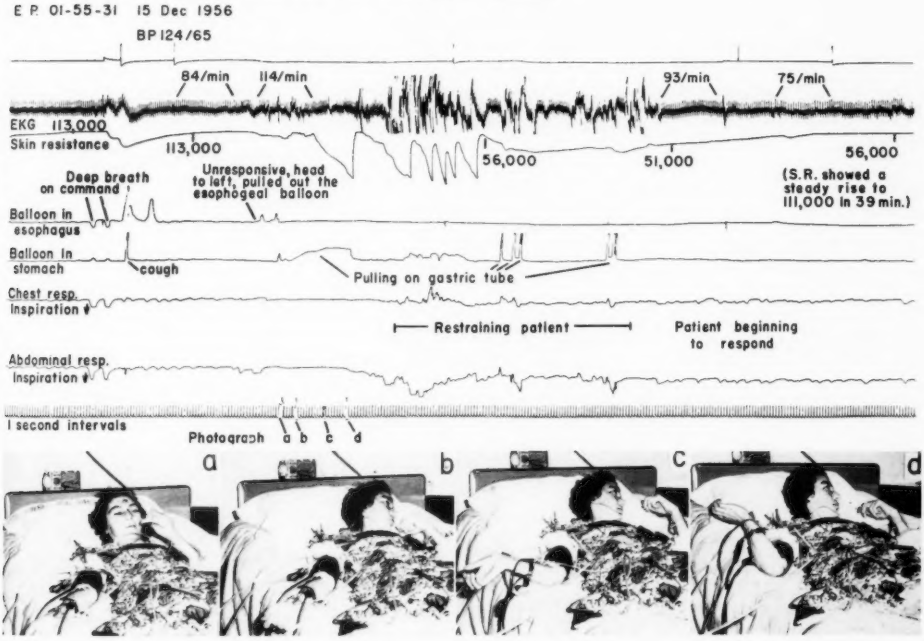


FIG. 2.—Spontaneous automatism. In this instance, expiratory apnœa, unresponsiveness and paroxysmal tachycardia came early in the seizure and were followed by fall of skin resistance.

*To illustrate article by J. M. Van Buren.*

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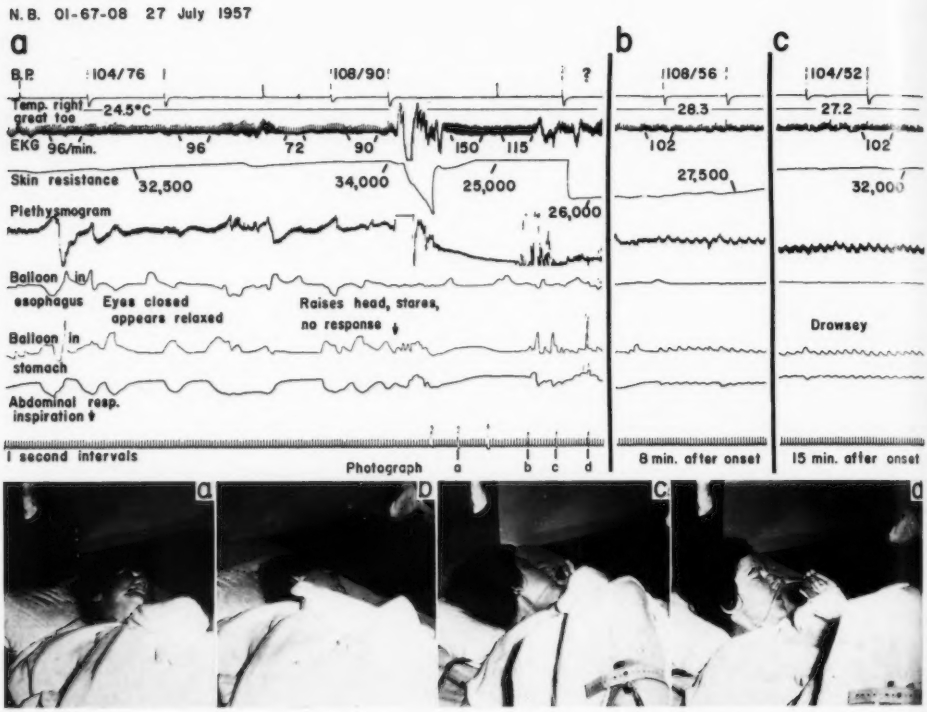



FIG. 3.—Spontaneous automatism. Prior to the attack, the toe temperature had been 24·5° ± ·3° C. for one half-hour. Six minutes following the attack the toe temperature was at a maximum of 28·5° C. and the subsequent fall is shown in samples B and C. The patient responded seven minutes after the onset of the attack and neither at this time nor subsequently was there any recall of the seizure.

*To illustrate article by J. M. Van Buren.*

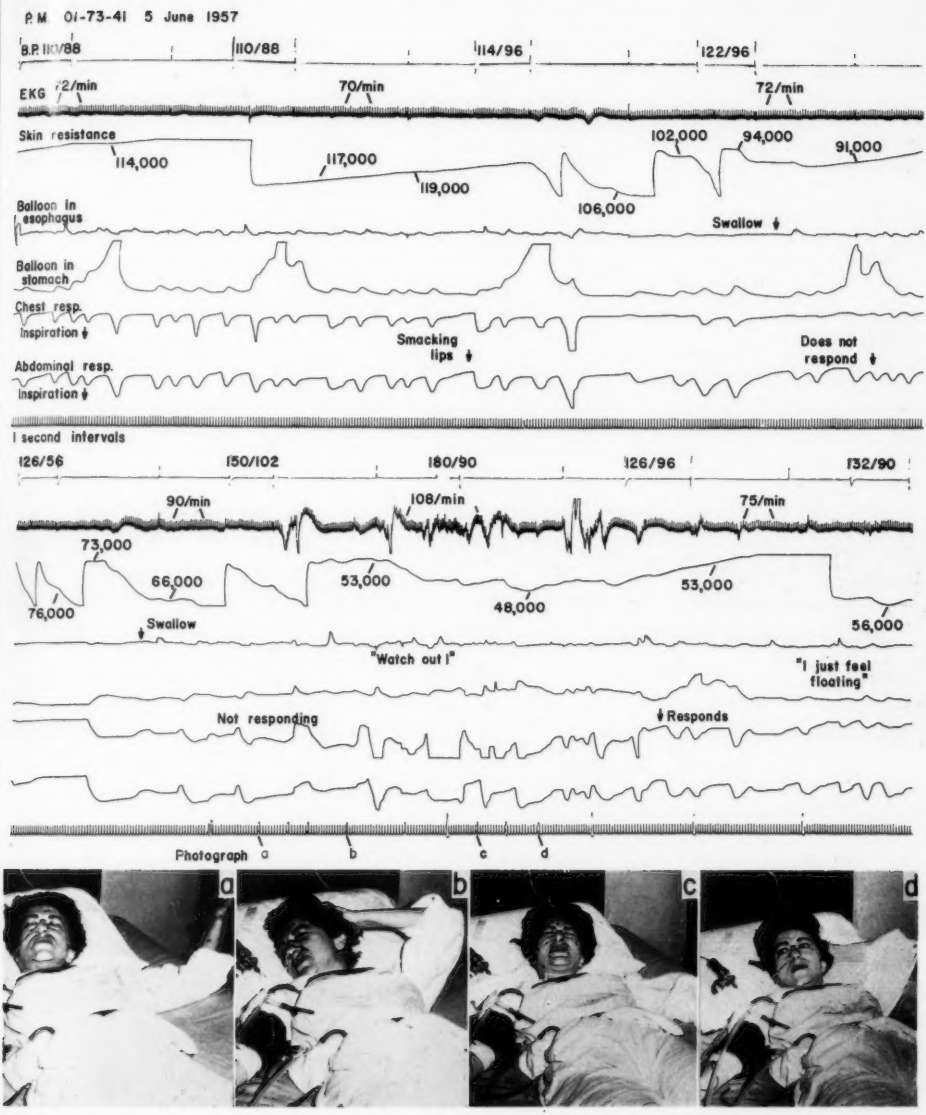



FIG. 4.—Spontaneous automatism. The two portions of the figure are consecutive. Note the two apparently separate episodes of skin resistance fall, one in the first and one in the second portion of the recording, with a slight tendency for recovery between. The gastric peristalsis gradually resumed its pre-ictal character in ten minutes following the above record.

*To illustrate article by J. M. Van Buren.*

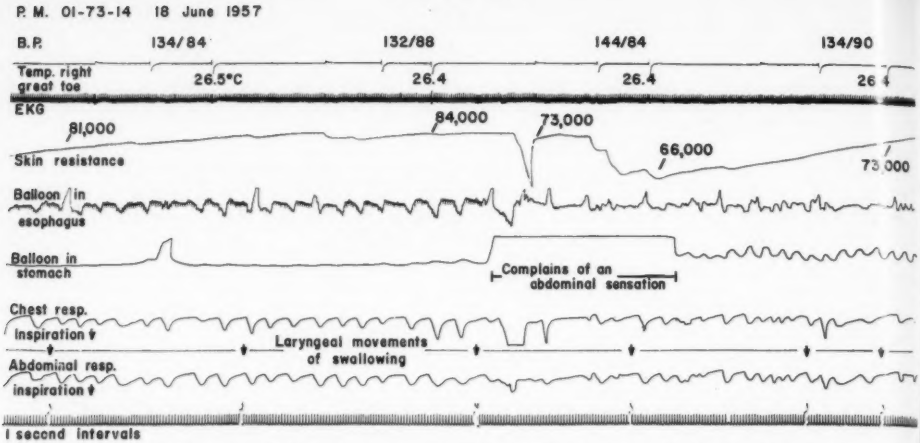
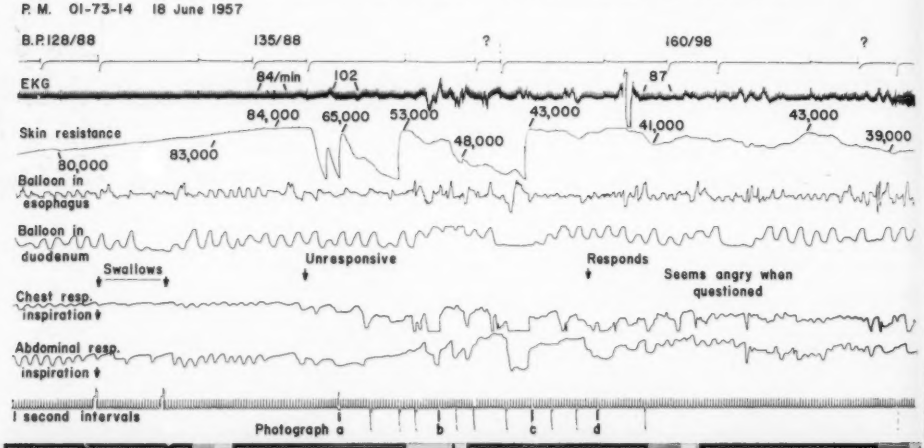



FIG. 5.—Passage of balloon from stomach to duodenum. Note the change in the recording of the œsophageal balloon. The end of a series of gastric contractions was seen prior to the prolonged and powerful pressure increase as the balloon passed through the pylorus. At this time the patient noted an epigastric sensation resembling her aura. In the latter part of the record, the faster duodenal contractions were recorded. When the balloon was withdrawn it was coloured with bright bile.



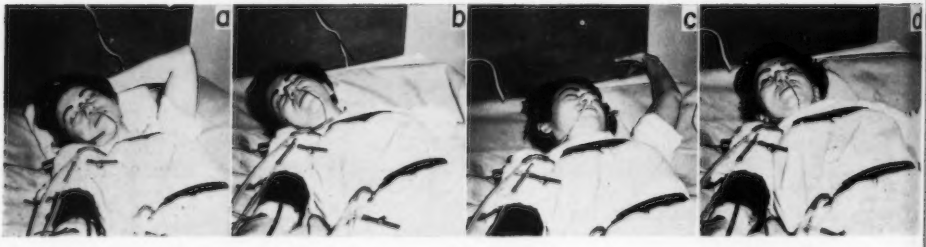




FIG. 6.—Spontaneous automatism. Balloon in duodenum. Note the precipitous skin resistance fall and the burst of tachycardia early in the seizure. The temperature of the plantar aspect of the right great toe was 26·3° C. at the start of the present recording. Between six and seven minutes following the termination of the attack the temperature had risen to 27·8° C. at which time skin resistance was 47,000 ohms. Following this, there was a fall in skin temperature as the skin resistance steadily rose.

*To illustrate article by J. M. Van Buren.*

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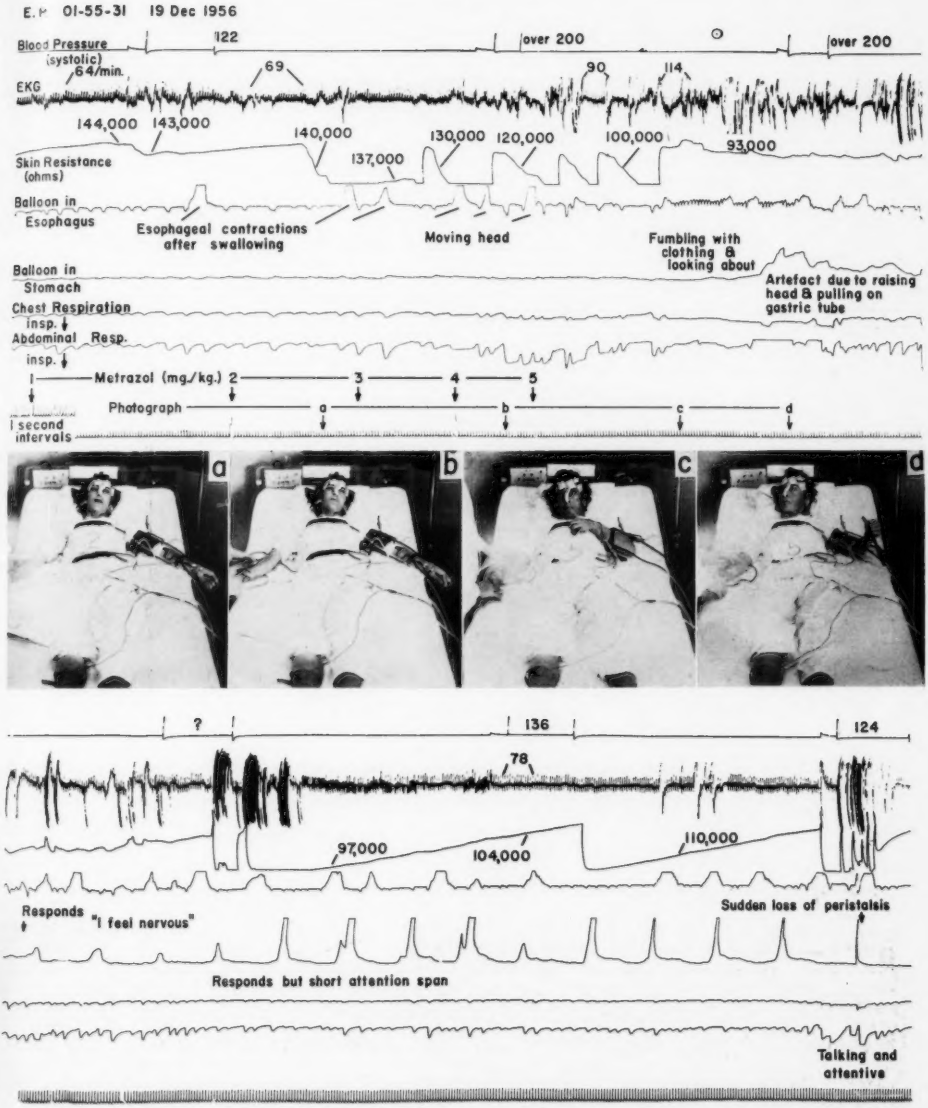


FIG. 7.—Metrazol induced automatism. Note the paroxysmal nature of the tachycardia coincident with photograph c. Only the systolic blood pressures are recorded. The apparent post-ictal gastric motor response was considered due to displacement of the balloon into the cardia or œsophagus by the patient (*see* text).

*To illustrate article by J. M. Van Buren.*

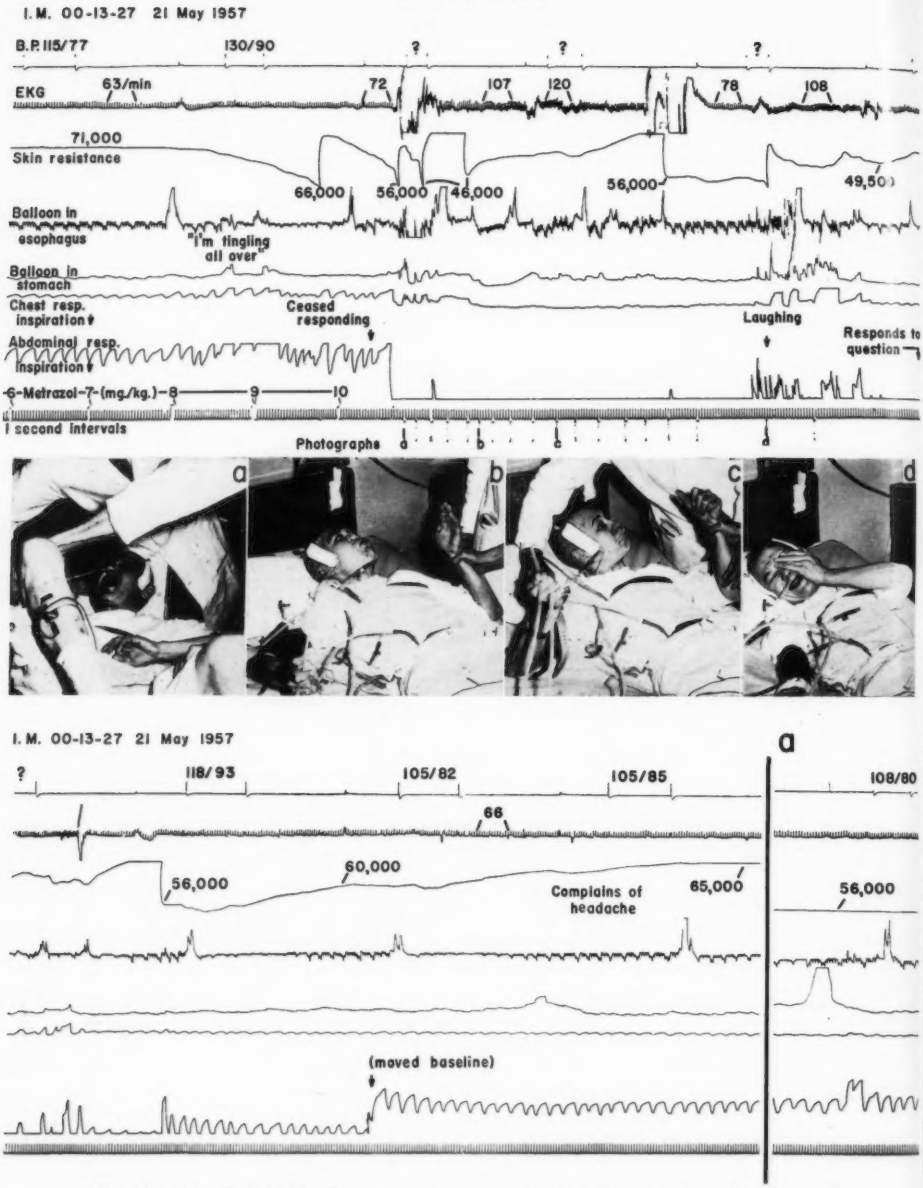


FIG. 8.—Metrazol induced automatism. Despite the violent nature of the patient's movements, as in photograph (*a*) they are well co-ordinated and were not those of a general seizure. The paroxysmal nature of the tachycardia is to be noted, especially that (108) in latter part of tracing when the patient was quiet. A feeble gastric contraction was seen in the post-ictal period just prior to her complaint of headache. A, A sample of a well-developed gastric contraction seen earlier in the tracing and prior to seizure induction by metrazol.

*To illustrate article by J. M. Van Buren.*

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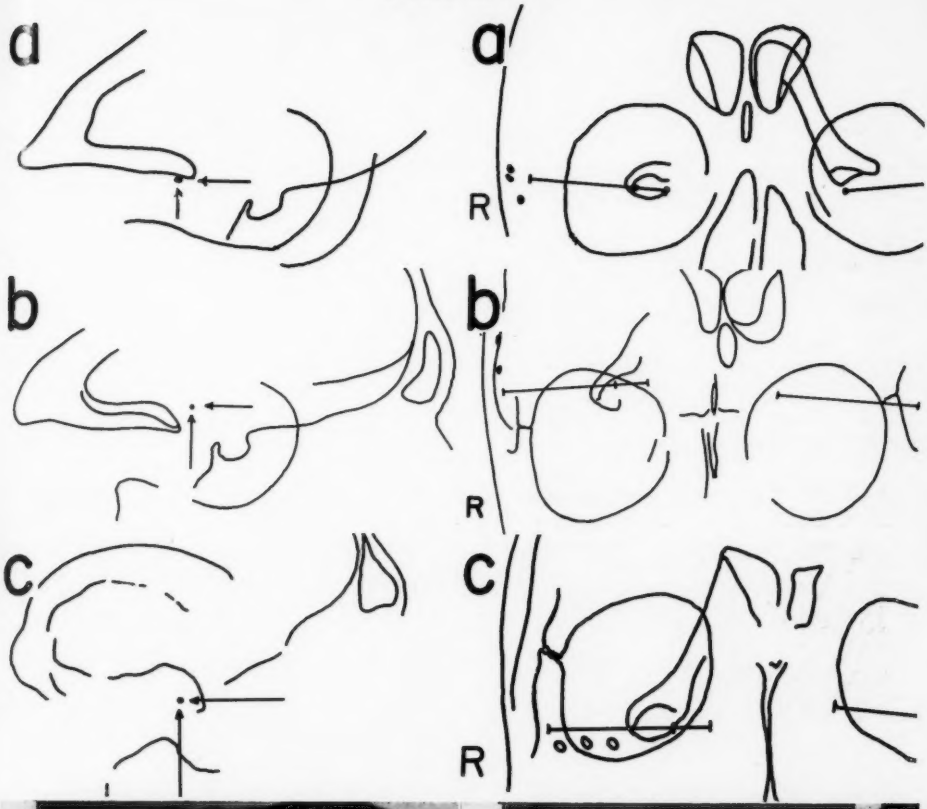


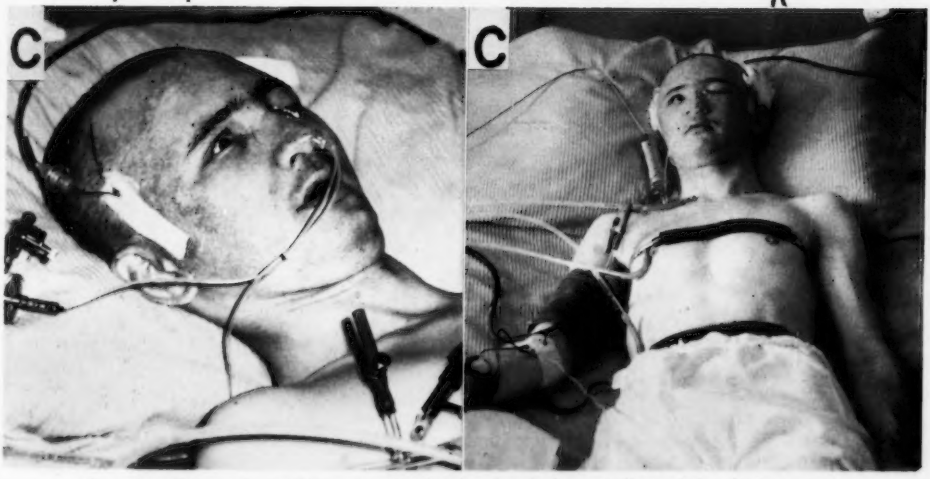


FIG. 9.—Electrode positions in the depth stimulation studies. Stimulations were carried out on the right side between the tip and a point 10 mm. from the tip of the 4 cm. electrode. The line drawings are tracings of the X-ray films taken after filling the ventricles with air (cf. Van Buren, in press). A, pes hippocampus (G. T., figs. 12 and 13); B, anterior portion of amygdaloid nucleus (I. M., fig. 10); C, vicinity of pes hippocampus. Note dilated tip of temporal horn. Photographs show the eye movement suggesting current spread to third cranial nerve (E. S., fig. 11).

*To illustrate article by J. M. Van Buren.*

PLATE LXXV

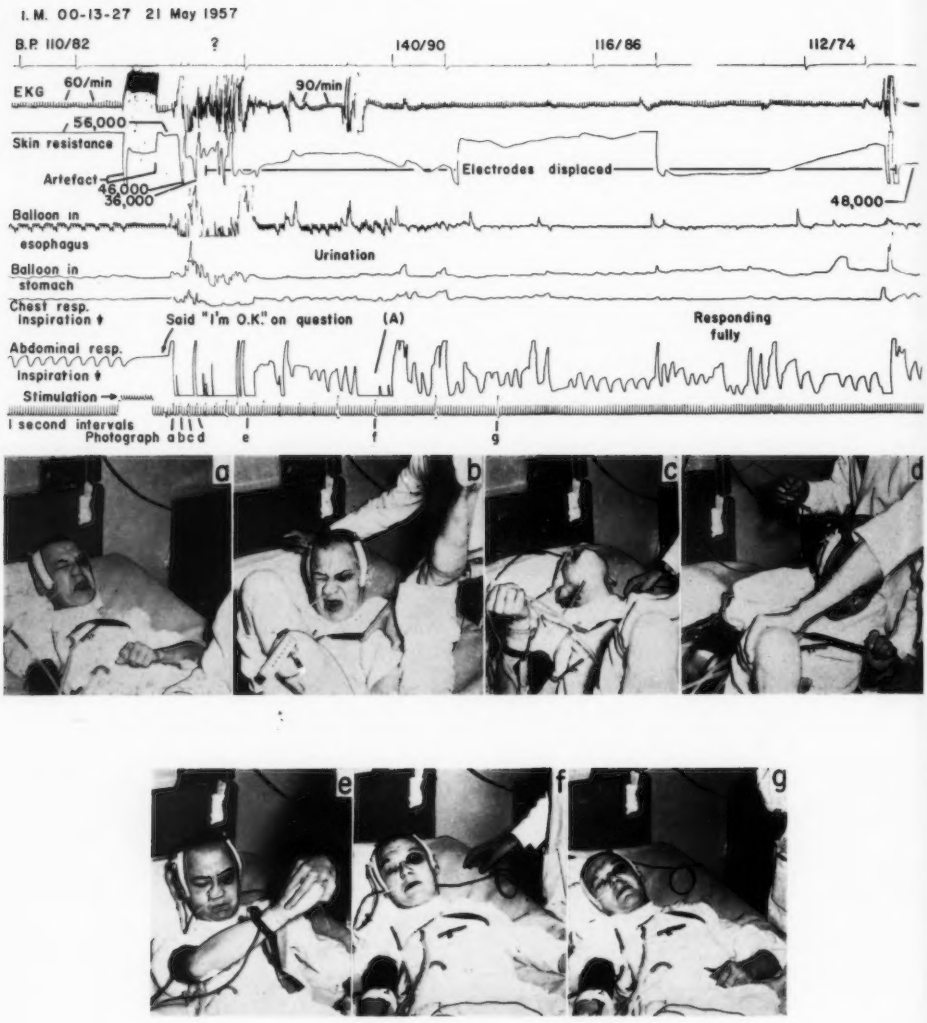


FIG. 10.—Automatism induced by stimulation in the anterior portion of the right amygdaloid nucleus. 10 V, 2·5 ms, 60 per second square wave pulses, 0·9–1·2 mA. Note the verbal response which occurred during expiratory apnea. At the point (A) the patient remarked "This monkey ought to have bigger horns than this." This attack was quite typical of her spontaneous attacks and is to be compared with the metrazol induced attack in fig. 8.

*To illustrate article by J. M. Van Buren.*

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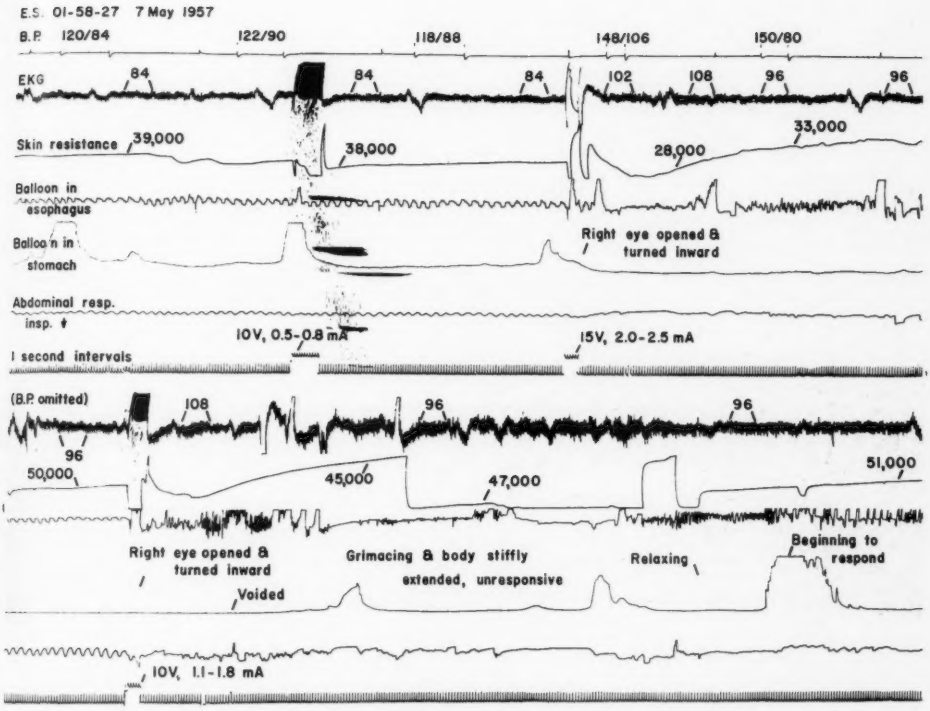


FIG. 11.—Stimulation with electrode implanted in the vicinity of the right pes hippocampus. Stimulations were carried out with square wave pulses, frequency of 60 per second, 2·5 millisecond pulse duration. The upper tracing contained a sub-threshold and a supra-threshold stimulation. The gastric peristalsis which had been regular in the half-hour prior to this stimulation was abolished. In the lower record the same point was stimulated 63 minutes later. Peristalsis was re-started for the three contractions shown and one subsequent one, then disappeared permanently for the remainder of the recording. The electrode position and photographs of the movement of the right eye are in fig. 9.

*To illustrate article by J. M. Van Buren.*

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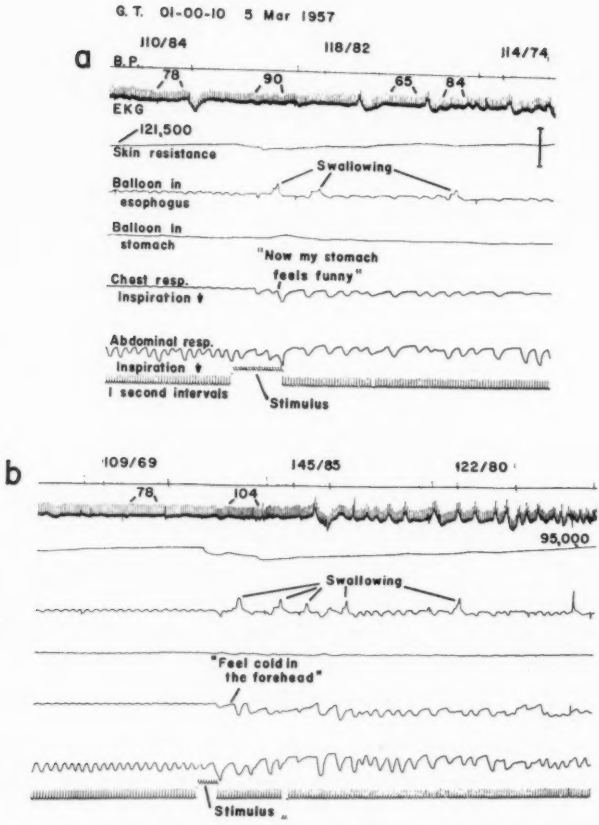


FIG. 12.—A, Stimulation in the right pes hippocampus 6 V., 2·5 ms., 60 square wave pulses per second, 0·5–1·2 mA. Stimulation resulted only in minor variations in the respiration, pulse and skin resistance followed by swallowing and the gastric sensation. The interval at the right of the skin resistance line equals 10,000 ohms. B, Stimulation of the same area with the same parameters but resulting in a maximum current flow of 1·9 mA. caused an intensification of the above autonomic symptoms and in addition hypertension. On subsequent questioning the patient reported that he had felt as though he might "pass out" during this stimulation (cf. fig. 9 for electrode position).

*To illustrate article by J. M. Van Buren.*

# PLATE LXXVIII

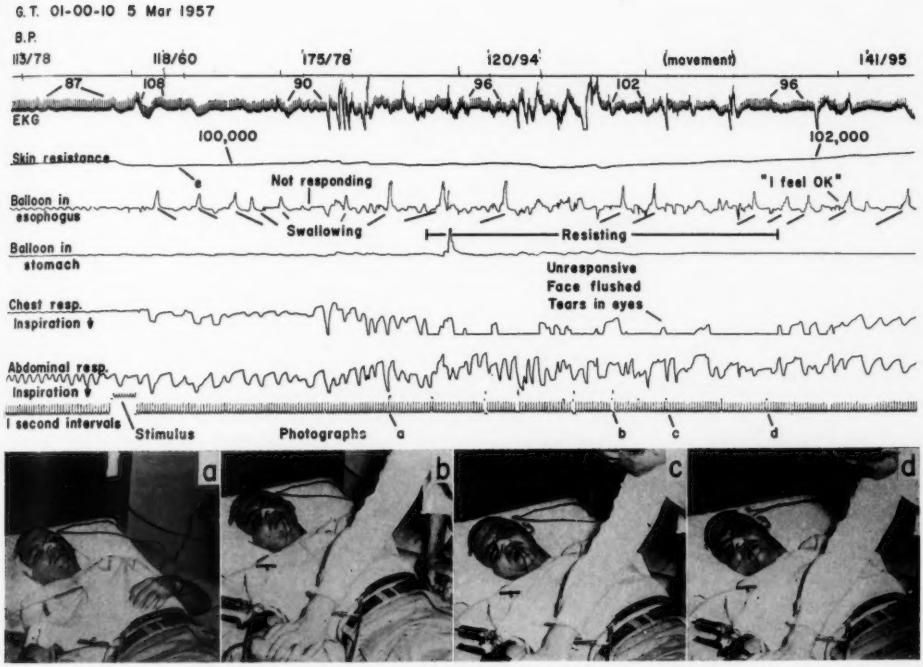


FIG. 13.—Stimulation of the right pes hippocampus with 6 V., 2·5 ms., 60 square wave pulses per second and current of 1·8 mA. An attack similar to the patient's habitual automatisms was induced. The long latency between stimulus and the loss of consciousness is of interest. At (E) he remarked, "I don't see so good out of my left eye." The autonomic changes are to be compared with those induced by stimulation of the same area in fig. 12 but which were unaccompanied by an automatism (cf. fig. 9 for electrode position).

*To illustrate article by J. M. Van Buren.*

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# VESTIBULOGENIC SEIZURES

## A Consideration of Vertiginous Seizures, with Particular Reference to Convulsions Produced by Stimulation of Labyrinthine Receptors

BY

SIMON BEHRMAN

AND

BARRY D. WYKE

*(From Regional Neurosurgical Centre, South East Metropolitan Regional Hospital Board, and The Department of Applied Physiology, Royal College of Surgeons of England)*

> "Epilepsy is plainly of two kinds: the first has a *centric* origin . . . ; the second is an affection of the reflex function, the exciting cause being *eccentric*, and acting chiefly upon the nerves . . ."
>
> "Causes of muscular contraction may be designated *centric*, as taking place at, or at least in a direction from, central parts of the nervous system. But there is another function the phenomena of which are of a totally different order . . . being excited by causes in a situation which is *eccentric* in the nervous system, that is distant from nervous centres. . . In this kind of muscular motion the motive influence . . . is excited by application of appropriate stimuli . . . to certain membranous parts, whence the impression is carried to the medulla, *reflected*, and reconducted . . ."
>
> Marshall Hall, 1833.

### Introduction

Sensory projections may be involved in seizures in two distinct ways. In the first, and more common category come those sensory hallucinatory phenomena (visual, auditory, olfactory, cutaneous, visceral and labyrinthine) which the patient experiences as a prelude to, or as a part of his seizure. In the second category—observed but rarely in clinical practice—come those cases whose seizures are provoked by stimulation of peripheral sensory receptors, such as those in the retina, cochlea, skin, or deeper tissues especially muscles and joints. On the other hand, in yet other cases such peripheral sensory stimulation may arrest the development of a seizure.

It is the thesis of this communication, exemplified by consideration of the vestibular system, that this clinical differentiation is of diagnostic significance. For we suggest that in cases in the first category the seizure

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discharges generally arise initially from irritated neurones situated in a primary cortical sensory projection sector; whereas in the second category the seizure discharges usually originate in the reticular nuclei of the brain-stem, when these nuclei are bombarded by afferent volleys of appropriate frequency from the peripheral receptors.

These two seizure mechanisms, as they affect the vestibular system, were recently considered by Behrman (1955) and to distinguish between these two categories use was made of the following terms: "Epileptic vertigo" to describe the ictal syndrome which we regard as being associated with discharge from the cortical projection sector of the vestibular system, and "vestibular epilepsy" to designate seizure responses to stimulation of peripheral vestibular receptors. However, such distinctions are not made by others, and the two terms may be used indiscriminately—or else the term "vestibular epilepsy" is applied to all cases of seizures in whom vertigo is a prominent feature of the symptomatology.

For these reasons, and in order to bring the terminology into line with that employed for the description of other types of seizures, we propose that the term "vestibular epilepsy" now be discarded, to be replaced by two terms each describing more precisely the role played by the vestibular projection system in the genesis of the ictus. It is suggested that the term *vestibular seizures* be used to designate the phenomena in those cases in which discharge from neurones within the cortical projection zone of the labyrinth is the essential feature of the developing seizure; and that *vestibulogenic seizures* be used to describe those rarer cases in which excitation of the receptors in the labyrinth leads to the development of seizures by evoking abnormal activity in the brain-stem nuclei. It is proposed that differentiation of these two categories is feasible clinically, and greatly facilitated by electroencephalographic study—and this is illustrated by the case report of an individual with vestibulogenic seizures. We further feel that similar considerations might be applied to all other varieties of so-called "reflex epilepsy," for reasons discussed in this paper.

## The Vestibular Projection Sector in the Cerebral Cortex and "Vestibular" Seizures

In order to justify the view, put forward in the introduction of this paper, as to the nature of *vestibular seizures*, it is necessary to identify a projection system from the labyrinth to a specific cortical sector, and to show that excitation of neurones in that cortical sector leads to sensory experiences similar to those normally evoked by stimulation of the labyrinthine receptors—and to seizures in appropriate cases. The most specific of such sensory experiences is vertigo—interpreted as a feeling of movement (usually rotation) of the patient's body in relation to his

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environment, or of his environment in relation to his body. There is also a less well-defined feeling of disturbed bodily equilibrium sometimes included under this heading—but to this the term "vertigo" is not properly applied (*see* Alpers, 1941), nor is it thus used in this communication.

In Penfield and Kristiansen's (1951) series of 222 cases with focal seizures, all of them operated upon with identification of the site of the irritable lesion, there were 81 patients whose seizures commenced by discharge of irritable neurones in a sensory projection sector of the cerebral cortex. In 9 of these cases the ictal sensory experience consisted of vertigo (as defined above); and in 8 of them the causal lesion—at whose borders lay the irritable neurones—was found in the posterior half of the superior temporal gyrus, or at the parieto-temporal junction. Electrical stimulation of these regions (Penfield and Rasmussen, 1950; Penfield and Jasper, 1954; Hécain, Penfield, Bertrand and Malmo, 1956; Penfield, 1957) produced vertiginous experiences similar to those occurring during spontaneous seizures. These findings suggest that in man there may be a vestibular cortical projection sector in the superior temporal gyrus, posterior to the primary acoustic sector on its dorsal bank. On the other hand, in Wyke's (1958) series of 56 cases with verified lesions in the temporal lobe 4 patients experienced vertiginous seizures; but in none of them was the lesion in the posterior temporal segment. Instead, in each case the lesion (and the irritable tissue at its borders) was confined to the middle third of the temporal lobe, mainly on its lateral aspect. These observations suggest that the vestibular projection sector may extend forwards from behind the primary acoustic sector to lie below and lateral to it in the superior temporal gyrus.

The results of anatomical and physiological investigation of this problem in experimental animals have long been equivocal; but recent studies permit a more confident analysis of the vestibulocortical projection system than has been possible previously. Early workers were often confused by the diffuse changes in cerebral electrical activity that occur with labyrinthine excitation (*q.v.*), and frequently doubted the existence of a specific cortical projection sector for the vestibular system. But identification of a dual ascending projection system for the vestibular (as for other) sensory systems has resolved many of these difficulties; and it is now clear that impulses of vestibular origin produce diffuse changes in cortical activity by way of reticular relays (*q.v.*), as well as more localized changes in a primary projection zone in the temporal lobe (or homologous area).

Early experiments by Aronson (1933), Spiegel (1934) and Gerebtzoff (1939, 1940) in cats suggested that the vestibular projection sector lay in the posterior parts of the suprasylvian and/or ectosylvian gyri, the projection system being mainly ipsilateral (Gerebtzoff, 1939) and inde-

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pendent of cerebellar relays (Price and Spiegel, 1937). However, Walzl and Mountcastle (1949), employing the evoked potential technique in cats, found the vestibulocortical projections to be mainly (but not exclusively) contralateral, terminating within the anterior bank of the anterior descending limb of the suprasylvian gyrus of the opposite hemisphere. Then Kempinsky (1951) analysing, in cats and monkeys, cortical potentials evoked by rotation and by direct excitation of the eighth nerve before and after cochlear ablation and section of the facial nerve, found the projection system to be bilateral—but he again described the cortical sector in question as involving the anterior descending limb of the suprasylvian gyrus, pointing out that this lies anterior to the sector suggested earlier by Aronson, Spiegel and Gerebtzoff (*loc. cit.*).

More recently Mickle (1953) and Mickle and Ades (1954) have identified (in cats) the cortical vestibular sector as lying in the posterior bank of the anterior suprasylvian gyrus, the anterior bank of the anterior ectosylvian gyrus and in the floor of the intervening sulcus (i.e. at the lower posterior part of the primary acoustic area). They find the vestibulocortical fibres to arise mainly from the superior vestibular nucleus, whence they cross the mid-line with the trapezoid fibres to turn rostrally to the thalamus in company with the medial lemniscus.

In the posterolateral ventral nucleus of the thalamus (in its lateral portion, just medial to the medial geniculate body) corticipetal fibres arise and pass to the cortical zone described above. Thus the primary vestibulocortical projection system, originally considered to be ipsilateral, then contralateral and finally bilateral is now believed to be mainly contralaterally directed (*see also* Andersson and Gernandt, 1954). Mickle and Ades (1954) further point out that direct excitation of one vestibular nerve leads to activation of the ipsilateral vestibular nuclei only. This supports an earlier finding by Gernandt (1949, 1953), that rotatory stimulation of the labyrinth leads to increased discharge only in the ipsilateral vestibulospinal tract, there being few interconnexions between the two sets of vestibular nuclei (Gernandt and Thulin, 1952; Thulin, 1953).

In the light of these studies it now appears probable that in man impulses from each labyrinth are conducted to the vestibular nuclear complex of the same side, whence they are directed across the brain-stem in second-order neurones terminating in the contralateral posterior (lateral) ventral thalamus. Third-order neurones thence relay to the para-acoustic cortex in the superior temporal gyrus, to a sector lying posterolateral and posterior to the primary acoustic cortex in Henschl's gyrus.

Irritation of neurones within this projection sector may thus give rise to *vestibular seizures*—in the sense defined above—the predominant subjective feature of which is vertigo. The seizure sequence may then

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progress through various other psychical, sensory and motor seizure phenomena, even to a generalized convulsion. In the electroencephalogram such seizure discharges are usually asymmetrical, at least at the onset, with perhaps a fast wave focal abnormality in the temporal region. These seizures occur as a rule in the absence of peripheral sensory stimulation and Carmichael *et al.* (1954, 1956) did not report any seizures on caloric stimulation among 73 subjects with unilateral supratentorial lesions. However, adequate stimulation of the contralateral labyrinth may very rarely excite such seizures as reported by Stauder (1934). Caloric stimulation of one labyrinth provoked in an epileptic subject a seizure associated with panoramic visual hallucinations, resembling in every way those occurring in the course of spontaneous seizures. Although lesions in the vestibular projection area can be revealed by special tests (e.g. Carmichael *et al.*, 1954, 1956; Hallpike, 1956), disturbances of vestibular reflex function—as nystagmus for example—are not features of vestibular seizures.

## The Vestibulo-reticular Projection System, and "Vestibulogenic" Seizures

Gernandt (1952) found that vestibular discharge evoked by rotation led to discharge bilaterally in the recticulospinal tract, and hence he suggested that each vestibule projects to both reticular complexes. It was further proposed (Gernandt and Thulin, 1952) that while there are few interconnexions between the vestibular nuclei of the two sides, each reticular complex receives afferents from both sets of vestibular nuclei—discharge from these leading to facilitation of some reticular units and inhibition of others. Similar results were obtained during direct stimulation of the vestibular nuclei by Thulin (1953); and by Mickle and Ades (1954) with stimulation of the exposed eighth nerve. Further, Roger *et al.* (1956) have shown that division of both eighth nerves, which abolishes their normal continuous discharge (Lowenstein and Sand, 1940; Adrian, 1943; Gernandt, 1949), diminishes reticular activation—in contrast to its increase when these nerves are moderately stimulated. Activation of the reticular system by caloric stimulation of the labyrinth in animals has also been demonstrated (Kirstein, 1953).

With this evidence, of bilateral reticular projections from the vestibular nuclei it may now be asked whether there is direct evidence of the influence of vestibular discharge upon reticulocortical activation.

That such influences exist is suggested by the fact that whereas the latency of cortical responses to vestibular activation in cats is some 6 to 8 msec. (Mickle, 1953; Andersson and Gernandt, 1954) in the primary projection area, in all other cortical areas this value is 14 msec. or more (Mickle, 1953). This indicates that the diffuse, non-specific cortical responses to vestibular discharge may be dependent upon



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transmission through pathways containing many more synapses than are present in the direct projection system (*vid. sup.*). Andersson and Gernandt (1954) also find that whereas liminal stimulation of the vestibular nerves leads to contralateral localized evoked potentials through the short latency path, more intense stimulation produces diffuse cortical activation bilaterally. Gerebtzoff (1939) demonstrated, in *encéphalé isolée* cats, that rotation of the animal led to a rapid, diffuse increase in the frequency and amplitude of cortical potentials that died away with rotation at constant speed, to reappear with deceleration. Moreover, if the animal were in a drowsy state rotation roused it at the same time as it increased the electroencephalographic activity. In such animals division of the eighth nerves leads to slowing and periodic spindling of the alpha rhythm (Roger *et al.*, 1956), whereas their direct stimulation produces activation of the electroencephalogram and arousal of the dormant animal. Finally, caloric stimulation of the labyrinth in man has been shown to produce an increase in the frequency of cerebral electrical activity in all areas of the brain (Baudouin and Caussè, 1943).

These observations leave little doubt, then, that volleys of impulses delivered to the reticular nuclear complex from the vestibular system are capable of modifying its influence on the cerebral cortex in certain circumstances, as evidenced by their arousal of the drowsing subject and evocation of diffuse, bilateral activation of the electroencephalogram. It now remains to enquire whether, under appropriate circumstances, such reticulocortical activation might lead to the production of seizures—seizures which we would designate *vestibulogenic* when evoked by vestibular stimulation.

That such is the case in animals has been clearly established with a variety of sensory stimuli. Thus Arduini and Lairy-Bounes (1952), using *encéphale isolée* cats, have demonstrated evocation of electroencephalographic seizure discharges from the reticular system by peripheral stimulation of a variety of sensory receptors; while earlier studies by Gellhorn and Ballin (1948) on narcotized cats given picrotoxin showed that whereas gentle sensory stimulation led to desynchronization of electroencephalographic activity, more intense stimulation produced seizure discharges in the upper brain-stem that were soon followed by paroxysmal activity in the cerebral cortex.

But not until the more recent work (e.g. Arduini and Lairy-Bounes, 1952) on the effects of projection of afferent volleys into the reticular system was it realized that these so-called "reflex" seizures depend primarily upon production of synchronized hyperactivity in the diffuse reticulocortical system, rather than upon activation of the specific thalamocortical systems (*see* Lairy, 1956). For no matter what specific cortical projection sector is strychninized in an animal, adequate stimulation of any peripheral sensory receptor will lead to electrical seizure

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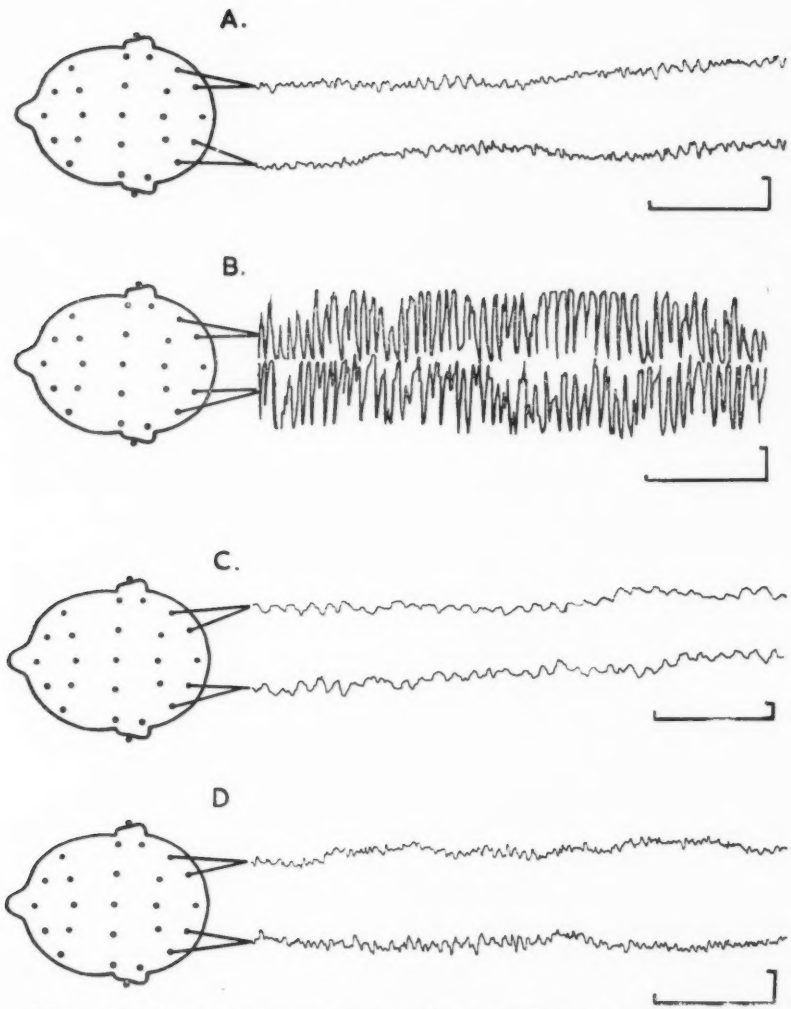


FIG. 1.—Sample strips from an electroencephalogram obtained during induction of vestibulogenic seizures by caloric stimulation of the left ear with water at 30° C. A, Record immediately prior to irrigation of ear. B, Record 45 sec. after commencing irrigation of left ear, and 5 sec. after completing it. The patient is unconscious, and having a generalized seizure with jerking of all four limbs. The convulsions began 20 sec. after commencing irrigation, and lasted 70 sec. C, Record 100 sec. after commencing irrigation, and 60 sec. after completing it. The patient is still unconscious, but the convulsions have stopped except for occasional twitching in the muscles of the right forearm. D, Record 6·5 min. after completing irrigation. The patient is now conscious, but complains of severe headache, vertigo and tinnitus. All muscular convulsive activity has ceased. Vertical line=50 $\mu$V. Horizontal line=1 sec. Note that calibration in strip C differs from that in strips A, B, and D.

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activity in the cortex (Arduini and Lairy-Bounes, 1952). On the other hand, chemical stimulation of a cortical sector with acetylcholine does not lead to seizures on peripheral stimulation, unless a reticular stimulant such as Metrazol be given also (Forster and Madow, 1950); while it is well known that in man the convulsive effects of cortical irritation (Walker, 1949), or of photic stimulation (Gastaut, 1954), may be greatly potentiated if the reticular system be simultaneously activated with Metrazol.

These findings make it clear then, that peripheral sensory stimulation (including stimulation of the labyrinthine receptors) may or may not evoke seizure phenomena, depending upon whether or not the afferent volleys evoke convulsive activation of the reticulocortical system. The production of seizures under these circumstances does not arise from abnormality in the primary thalamocortical system or its projection area; nor does it necessarily result from any hypersensitivity of the particular peripheral receptors concerned. Instead, the principal criterion is the extent to which the afferent volleys induce synchronized hyperactivity in the reticular system of the brain-stem (*see* Li *et al.*, 1952), a system into which all afferent pathways (including those from the vestibule) project and whose response to afferent volleys is indicated in the electroencephalogram as bilaterally synchronous variations in voltage and frequency of cerebral electrical activity.

For this reason, seizures induced by vestibular stimulation (*vestibulogenic seizures*) belong to the same physiological order of seizures as do those resulting from any other form of sensory activation (such as "photogenic," "audiogenic," or other type of so-called "reflex" seizure) in that they depend upon the initiation of convulsive activity in the reticulocortical system by abnormal activation of the reticular system. That such is the case is evidenced by the electroencephalographic findings in a case of vestibulogenic seizures, presented below. In this patient, the threshold of the labyrinthine receptors was within the normal range (as indicated by caloric evocation of vestibular reflex disturbance), but labyrinthine stimulation in either ear produced convulsions with loss of consciousness and widespread, bilaterally synchronous seizure discharges in the electroencephalogram (fig. 1).

## Cases of Vestibulogenic Seizures

It is probably significant that the few reports in the literature concerning provocation of seizures by labyrinthine stimulation, relate to patients who like our own, were known to be subject to seizures (Marie and Pierre, 1922; Jones, 1923; Rabinowitsch, 1928; Scheinmann, 1928; Stauder, 1934). Reference to one of these cases has already been made. In this subject the ictal characteristics suggested temporal lobe epilepsy and the seizure provoked by labyrinthine stimulation was most probably

of vestibular nature (Stauder, 1934). Unfortunately the information given by the various authors concerning the remaining 15 subjects is insufficient for classification. Since 8 of these subjects were young men liable to military service for which they were fit but for epilepsy, it may perhaps be permissible to conclude that a proportion of the provoked seizures were probably of vestibulogenic nature.

Basing his views on observations on 5 patients exhibiting recurrent seizures with post-ictal vertigo or dysequilibrium, with or without tinnitus, Behrman (1955) concluded that it is possible by clinical analysis to differentiate a syndrome comprising recurrent epileptic seizures provoked by paroxysmal vertigo of labyrinthine origin. He also adduced evidence that the vestibulogenic seizure is "a sub-group of sensorily precipitated epilepsy, i.e. epilepsy provoked under certain circumstances in constitutionally predisposed individuals by the stimulation of various types of receptors."

We report here a case in which caloric stimulation of the labyrinth provoked seizures repeatedly, and in whom electroencephalographic studies revealed caloric evocation of seizure discharges associated with the overt convulsions. As far as we know, this is the first occasion on which such an electroencephalographic observation has been reported with vestibular stimulation in man.

*Case Report.*—The patient (No. 6307), a 58-year-old school janitor, was admitted on 3.6.56, because he had had five fits in the previous twelve hours.

In 1939 he had developed swelling of the right side of his face and neck, which subsided but recurred in 1941. He was told it was erysipelas. This was followed by episodic attacks of vertigo, during which he sometimes fell and became unconscious for a brief period. In 1942 he developed a throbbing dull ache in his right temple which spread down the right side of his neck—this occurred up to five times a week and persisted until his admission. In 1951 he had three generalized seizures, following which he was given phenobarbitone $\frac{1}{2}$ gr. t.d.s.

In spite of this he began, the following year, to experience a more complex seizure sequence; and he began to complain of tinnitus and impaired hearing in his left ear. These seizures continued up to the time of his admission, and numbers of them were witnessed by his wife and son.

The seizures begin with a sensation like a tight band around his head which lasts for about thirty minutes, increasing in intensity and waking him when he is asleep. This is associated with vertigo and ataxia, an increasingly loud noise like a dynamo in his left ear, and gradually developing mental confusion. He feels that his environment is rocking around him, his gait becomes staggering and he has to seek support, otherwise he would fall. Then he gives a choking cry, abducts both arms with the fists clenched, and loses consciousness; following this he flexes his arms, and puts his hand to his head. His arms continue to flex and extend in this way alternately for about two to three minutes, during which period his eyelids open and his eyeballs rotate upwards. Sometimes his face is flushed at this stage; but at other times he is deathly pale. Next the arm movements subside, while his head rotates from side to side and both his legs jerk. Finally his head becomes stationary and deviated to the left, while his limbs become limp and he hyperventilates for a few minutes. The panting gradually

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subsides, and he slowly regains consciousness over the next half-hour to an hour. He then falls into a deep sleep lasting three to four hours. There is never any incontinence.

At first (i.e. in 1952) these seizures occurred only about every three months. But in spite of medication (at first with phenobarbitone, and then with Epanutin and phenobarbitone) their frequency slowly increased to several per day until admission. Most of the seizures occurred in the early hours of the morning while the patient was asleep; but others have occurred at random at all hours of the day and night.

In the two months prior to admission he had complained of some weakness of his right arm and leg; and this was associated with increasing prominence of movements of these limbs during the seizures. Until 1956 the ictal movements of the limbs had been symmetrical; but in the last few months it was noticed that these movements were becoming much less marked in the left limbs than in the right.

Examination in June 19, 1956 (on admission following a series of seizures) revealed relative weakness of the right arm and leg. All reflexes were symmetrical. The gait deviated to the right, and the trunk inclined to the right when standing. Both plantar reflexes were flexor. The blood pressure was 180/100, with hypertrophy of the left ventricle. The results of examination of the blood were normal. Skull radiographs revealed no abnormality.

Caloric tests on the right (12.6.56) and left (24.6.56) ears disclosed normally sensitive labyrinths on each side, but produced a seizure in each case. The ears were irrigated with water at 30° C., with a flow rate of 3 ml. per second. Nystagmus was produced on each occasion at about three minutes. However, during irrigation of the right ear severe headache developed during the fourth minute, together with jerking of the right arm that spread rapidly into the right leg. At the same time the patient lost consciousness, and remained unresponsive for a further four minutes. He then recovered consciousness, but was still drowsy and confused for another thirty minutes. He complained of continuing vertigo during this period. He was not incontinent. The ictal sequence of events following irrigation of the left ear differed in no way from the above description—and in particular, the convuslive movements still involved the right limbs.

Electroencephalographic studies were performed on 26.7.56 (*see* fig. 1). The resting record revealed a low-voltage alpha rhythm at 10–11 cps., considerable beta activity in the fronto-temporal areas, and some theta instability in the temporal regions that was increased by hyperventilation. There was no paroxysmal activity, and no evidence of any localized lesion. All activity was bilaterally symmetrical.

Recording was continued on the transverse leads during caloric stimulation of the left ear with water at 30° C. at the same flow rate as before. For the first 15 seconds no change was observed—then the alpha rhythm increased in amplitude and accelerated to 12 to 13 cps. Shortly after, bilaterally synchronous paroxysms of activity at 6 cps. emerged, and the patient complained of severe vertigo and appeared confused: at 22 seconds these phenomena were accompanied by jerking movements of the right hand. Within a further one to two seconds the convulsion involved the right leg as well, and the patient lost consciousness, with spread of the 6 cps. activity from the temporal leads to involve all areas of the brain. This discharge continued for two minutes, until it suddenly ceased and the patient regained consciousness, the record returning to its pre-irrigation pattern immediately. The patient was slightly confused on recovery, and complained of vertigo.

In order to facilitate the differential diagnosis of the two syndromes of *vestibular seizures* and *vestibulogenic seizures*—a distinction which has important implications for planning the investigation and treatment of a case of vertiginous seizures, we propose the following as a tentative

summary of the principal clinical features of the two syndromes. However, we appreciate that these suggestions may require later revision as our experience in this field widens: as they stand at present, they are based on the data presented in this paper, and in Behrman (1955) and Wyke (1958).

A. *Vestibular Seizures*

These are ictal disturbances of varying degrees of severity in which vertigo is a prominent feature, that arise from paroxysmal firing of hyperexcitable neurones in the mid-temporal cortex. The principal features are:

(1) Sudden onset of severe vertigo is the initial event of the ictus.

(2) Tinnitus which is often unilateral, accompanies, or even precedes the vertigo.

(3) There is a variable progression through other psychical, sensory and motor ictal phenomena; and the motor phenomena consist in twitching in muscle groups mainly in one upper limb, and in the head and neck.

(4) Consciousness may or may not be lost—frequently it is not.

(5) There is little or no clinical evidence of disordered vestibular reflex function before or during the ictus.

(6) Asymmetrical, or focal electroencephalographic abnormalities occur during the seizure, and are sometimes present in the inter-ictal period.

(7) Post-ictal vertigo is not experienced.

(8) An irritative cortical lesion is present in one or other temporal lobe.

(9) Seizures are but rarely provoked by direct stimulation of the labyrinth, and then only from the ear contralateral to the temporal lesion.

(10) Inter-ictal disorders of vestibular function are not in evidence.

B. *Vestibulogenic Seizures*

These are ictal disturbances, usually of considerable severity, that arise from paroxysmal firing of hyperexcitable neurones in the brain-stem reticular system, induced by vestibular discharge. Their principal features are:

(1) Onset of vertigo of varying severity in the ictus, sometimes increasing steadily in intensity.

(2) Tinnitus less often accompanies the vertigo, and rarely precedes it.

(3) Progression to other ictal sensory phenomena is rare. Progression to motor ictal phenomena is common; but it consists in myoclonic jerking of the limbs, often bilateral but sometimes unilateral.

(4) Consciousness is usually lost.

(5) Clinical evidence of disordered vestibular reflex function during the ictus is provided by ataxia, ocular deviation, nystagmus, and tilting or rotation of the head.

(6) Electroencephalographic abnormalities during the seizure are

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bilaterally synchronous and more or less symmetrical. Such abnormalities are much less evident, or are absent, in the inter-ictal period.

(7) Post-ictal vertigo may be experienced.

(8) No cortical lesion is present.

(9) Seizures may be provoked by stimulation of the labyrinth in either ear.

(10) Inter-ictal disorders of vestibular function often in evidence.

*Differential Diagnosis*

The association of vertigo or dysequilibrium and loss of consciousness is, of course, not uncommon and can occur in a variety of disorders which call for consideration (*see* Behrman, 1955). Among them are hypoglycæmic state, carotid sinus seizures (*see* Behrman and Knight, 1956) and intermittent insufficiency of the basilar arterial system (Millikan and Siekert, 1955). Vestibulogenic seizures can occasionally be provoked by rotation of the head, and Kussmaul and Tenner's (1859) case is occasionally given as the earliest reported example of this. A boy of 12 with a "remarkable propensity to steal" also exhibited the peculiarity that strong rotary movements of his head would cause him to lose consciousness for periods of "remarkably short duration." An abnormal formation of the atlas on post-mortem examination led the authors to conjecture that the spinal foramen was greatly narrowed when the head was turned. The syndrome presented by this case bears a close resemblance to that reported by Ford (1952) and is, of course, quite unrelated to *vestibulogenic epilepsy*.

## Summary

(1) An attempt is made to differentiate between two types of vertiginous seizure (seizures in which vertigo is an early and prominent feature).

(2) *Vestibular seizures* are defined as seizures arising from discharge of neurones in the cortical projection sector of the labyrinth. Experimental and clinical data are reviewed to define the location and afferent connexions of this sector in man.

(3) *Vestibulogenic seizures* are defined as seizures arising from the brain-stem reticular system as a result of labyrinthine discharge. Experimental and clinical data are reviewed to define the vestibulo-reticular connexions, and their role in the production of seizures.

(4) A case is reported in which vestibular (caloric) stimulation repeatedly produced seizures with electroencephalographic features indicating their reticular origin.

(5) The clinical features of *vestibular seizures* and *vestibulogenic seizures* are compared and contrasted, in an attempt to facilitate their differential diagnosis.

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# TORULOSIS OF THE CENTRAL NERVOUS SYSTEM IN BRITAIN

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## INTRODUCTION

Torulosis, also known as cryptococcosis and European blastomycosis, is a fungal disease caused by *Cryptococcus neoformans* (*Torula histolytica*). Although the organism is widespread in nature and occurs throughout the world, the disease is rare in Britain and case reports from this country have been few. In the United States and Australia infection with this organism is commoner and there is a considerable literature from these countries.

Freeman (1931) reported on pathological material from 19 patients who had died from torulosis in the U.S.A. and found that only 40 cases had been recorded in the world literature. Fifteen years later Cox and Tolhurst collected over one hundred cases from the literature and published a further 13 case reports from Australia; their bibliography contained 134 references. The most recent monograph was published in 1956 by Littman and Zimmerman who reported on material from over 100 cases received by the Armed Forces Institute of Pathology in Washington and stated that there were now over 300 cases recorded in the world literature. These authors consider that the published reports "do not reflect the true incidence accurately, since, in the United States alone during a four-year period after 1949, 151 fatal cases were reported by the National Office of Vital Statistics." Reports from both the Johns Hopkins Hospital, Baltimore, and the Mount Sinai Hospital, New York, reveal that only 4 cases of the disease have been seen in each hospital in twenty years. Since the disease causes 30–40 deaths annually in the United States alone, Littman and Zimmerman believe that many cases are unrecognized clinically and are diagnosed only at post-mortem examination.

Although torulosis is the commonest fungal infection affecting the central nervous system it was not until 1894 that the first description of a verified case was given by Busse: however, Zenker had in 1861 reported a fungal disease affecting the brain which probably was torulosis (Freeman, 1931).

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## Review of British Cases

The first report of a case of torulosis occurring in Britain was by Smith and Crawford in 1930 and the second appeared eight years later (Greenfield, Martin and Moore, 1938). In both cases the diagnosis was made at post-mortem examination but in 1943 Blair reported the case of a patient who presented with psychiatric symptoms; C. neoformans was isolated during life from the cerebrospinal fluid (C.S.F.) but treatment was of no avail and the patient died three months after the first symptom. Magarey and Denton in 1948 reported the fourth case: the diagnosis made during life was tuberculous meningitis. In the following year, Daniel, Schiller and Vollum reported 2 further cases and stated ". . . there is little doubt that the condition is not so uncommon as this paucity of reports suggests". Symmers (1953) also stated that this mycosis was not as rare as was believed since he had seen 6 cases, 4 of which were ". . . straightforward examples of cryptococcal meningo-encephalitis"; he recorded fully the other 2 cases, 1 of which simulated Hodgkin's disease. Other cases of torulosis simulating Hodgkin's disease were published by Beck *et al.*, Levene and Michaels, and Misch (all in 1955). The only other report of torulosis occurring in Britain was by Caldwell and Raphael (1955) but no post-mortem examination was carried out. In the past twenty years 1,603 post-mortem examinations have been performed at the National Hospital, Queen Square, and only 2 of these revealed torulosis.

No reports of torulosis have been published in a British neurological journal and since ". . . cases may sometimes be missed through ignorance of the clinical and pathological features of this infection" (Blair, 1943) we are reporting here 3 recent cases, 2 of which were diagnosed during life.

## Case Reports

### (1) *Mrs. H. O.* (*N.H.Q.S. No.* 75264)

*Summary.*—A woman aged 70; six weeks' mild fever, four weeks' generalized headaches, anorexia and loss of memory; one week's diplopia. Left sixth and seventh cranial nerve palsies with signs of meningeal irritation. Cryptococci were seen and grown from C.S.F. Died ten weeks after onset of first symptom. Cryptococcal meningitis confirmed post mortem.

The patient, a housewife aged 70 years, was admitted to the National Hospital, Queen Square, under the care of Dr. Denis Williams on October 18, 1957. The history was obtained from her daughter who said that, while on holiday in the Isle of Wight, six weeks previously, her mother suddenly felt ill and shivery and went to bed early. She failed to improve over the next two days and returned to London where her doctor could find no abnormal signs except for a temperature of 102°F. The pyrexia persisted over the next few days but at a lower level and she stayed in bed most of each day, getting up for a few hours during the afternoon. Four weeks before admission to hospital she complained of mild generalized headaches, lost her

appetite and her memory became poor. One week before admission she complained of seeing double and developed a pain in her neck.

Examination on admission revealed a grossly disorientated woman who denied any disability and insisted that she was at her grandson's school waiting to take him home. She was able to give her correct age after considerable hesitation but did not know the year. There was tenderness over the right side of the occipital area; the left pupil was larger than the right but both reacted normally to light and accommodation; the left eye did not abduct fully and there was slight left lower facial weakness. There were no other signs in the central nervous system or elsewhere and her temperature was normal. During the next few days her general condition deteriorated and she developed neck stiffness with a positive Kernig's sign. In view of the findings of dementia, and left sixth and seventh nerve palsies in a woman of 70 it was thought that she had an intracranial neoplasm.

Investigations revealed a hæmoglobin of 15 grammes per 100 ml. (102 per cent), a white cell count of 7,000 per c.mm., polymorphs 85 per cent, lymphocytes 7 per cent and monocytes 8 per cent, and an erythrocyte sedimentation rate (E.S.R.) of 11 mm. in one hour. There was a faint trace of albumen in the urine together with a few leucocytes. X-rays of the chest and skull were normal. The C.S.F. pressure on lumbar puncture was over 300 mm. and there were 4 lymphocytes per c.mm.; the protein level was 80 mg. per 100 ml. and there was a typical "paretic" Lange curve (5443210000). The electro-encephalogram revealed bilateral theta activity with occasional slower waves within the delta range, chiefly on the left side, and from this it was concluded that there was evidence for a left-sided lesion, probably intracerebral.

Ventriculography on November 4 was normal. The ventricular C.S.F. contained 2 lymphocytes per c.mm., 50 mg. of protein per 100 ml., 80 mg. of sugar per 100 ml., 700 mg. of chlorides per 100 ml. as NaCl and the Lange curve was normal (0000000000). After staining with toluidine blue numerous cells were seen in the counting chamber: they were round with well-defined walls and, though variable in diameter, bore a superficial resemblance to red blood corpuscles. Some of them, however, were budding and others contained round or irregular masses.

Following ventriculography the patient became drowsier and vomited several times and on November 6 a ventricular drain was inserted. A repeat examination of the ventricular C.S.F. revealed that there was a pleocytosis of 26 per c.mm. (80 per cent lymphocytes and 20 per cent polymorphs) and there were 415 fungal organisms per c.mm. The C.S.F. contained 64 mg. of sugar per 100 ml., 660 mg. of chlorides per 100 ml. and the Lange curve was again normal.

In spite of treatment with antibiotics, including penicillin and aureomycin, her general condition deteriorated, the blood pressure fell and she died on November 11.

*Bacteriology.*—With nigrosin preparations (figs. 11 and 12) the organisms were seen in sharp relief against the dark background; each was surrounded by a clear broad halo, representing the capsule, which had not been visible in the counting chamber. The organisms were found to be Gram positive and the capsules Gram negative. Cultures from the centrifuged deposit gave a good growth on Sabouraud's medium after forty-eight hours, both at room temperature and at 37° C., the colonies being moist and creamy in appearance. Growth also took place after forty-eight hours in glucose broth and on blood agar. Two weeks after the inoculation of sugar media acid—but not gas—was produced, with glucose, saccharose and maltose; no fermentation occurred with arabinose, inositol, adonitol, lactose, dulcitol, mannite, salicin, fructose, inulin or galactose. A saline suspension of organisms obtained from the glucose broth culture was injected intraperitoneally into a mouse. The animal appeared to remain well but, when it was killed two weeks later, post-mortem examination revealed a firm, creamy-white nodule 0·5 cm. in diameter in the liver from which morphologically similar fungi were cultured; no other viscus was affected.

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A second mouse was killed six weeks after inoculation and although it appeared to remain well during life the post-mortem examination showed gross mesenteric involvement.

The characteristic capsular halo, the ability to grow at 37° C. as well as at room temperature, the fermentation of glucose with the production of acid but not gas, and the pathogenicity for mice are features which established the organism as *Cryptococcus neoformans* and this was subsequently confirmed by Dr. Jacqueline Walker of the Myocological Reference Laboratory.

When tested by the disc method the organism appeared to be insensitive to penicillin (2·5 international units), aureomycin (100 microgrammes), chloramphenicol (40 microgrammes) and streptomycin (80 microgrammes). Sensitivity to the antifungal agent Amphotericin B was examined by placing powder containing 100 microgrammes of this substance in a small trough cut out of the culture medium. This produced a zone of inhibition of growth measuring 1·5 cm. in diameter (fig. 16).

*Pathology.*—Post-mortem examination (Prof. W. Blackwood) revealed a nodule 3 mm. in diameter at the apex of the lower lobe of the right lung. The leptomeninges of the brain and spinal cord were distended by slightly cloudy, faintly greenish fluid; the fluid which ran out when they were incised contained minute globules immiscible with C.S.F. There was gelatinous material around the trigeminal ganglion and cranial nerves in the pituitary region. The lateral ventricles were symmetrically and markedly dilated. At the posterior end of the first temporal convolution on the right side a small cystic cavity filled with gelatinous fluid was present in the white matter immediately deep to the cortex (fig. 3).

*Microscopy.—Lungs:* The small subpleural nodule consists of dense strands of fibrous tissue whose interstices contain cryptococci, sometimes singly, more often in groups (fig. 5).

*Brain:* The leptomeninges are thickened by amorphous material in which cryptococci are embedded; in some areas these are innumerable and in others quite scanty. The Virchow-Robin (V.R.) spaces are grossly dilated by gelatinous material: the small cavity seen in the temporal lobe at post-mortem is such a dilated perivascular space cut transversely (fig. 6). There is a minimal cellular response to the infection, consisting of perivascular aggregations of lymphocytes, occasional giant cells and macrophages. The substance of the brain is normal apart from perivascular and pericellular œdema. There is no loss of myelin or ganglion cells and no increase in astrocytes. An interesting finding is the occurrence of several minute capillary varicosities in the substance of the temporal lobe.

*Pituitary:* Cryptococci, occasional giant cells and a few lymphocytes are seen surrounding the stalk and infiltrating the substance of the pituitary, particularly the posterior lobe.

*Spinal cord:* The leptomeninges are distended by loose tissue consisting of cryptococci and occasional perivascular aggregates of lymphocytes. In some areas the inflammatory cells around the veins are particularly numerous, amounting to a periphlebitis. In the substance of the spinal cord the nuclei of the anterior horn cells are displaced or have disappeared; there is a considerable quantity of lipofuchsin and the cytoplasm has in many instances become homogeneous and distended, with dissolution of the Nissl substance. The periodic acid-Schiff (PAS) technique stains the corpora amylacea of the spinal cord as well as the cryptococci. These have occasionally been confused with each other but the heavily-staining spherical corpora amylacea can be distinguished from the paler, slightly biconcave cryptococci (fig. 7).

*Posterior nerve root and ganglion:* the organisms are seen infiltrating and separating the nerve fasciculi; some nerve roots show patchy atrophy of fibres.

All the other organs, including the lymph glands, are histologically normal.

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(2) *Miss E. J.* (*M.V. No.* 39130).

*Summary.*—A woman aged 57; two weeks' occipital headache, dizziness and blurred vision; one week of weakness and unsteadiness of limbs. Defective memory, neck stiffness, bilateral papillœdema; right sixth cranial nerve palsy, bilateral cerebellar signs, right extensor plantar response. X-ray chest disclosed cavitating mass. Post-mortem revealed pulmonary and cerebral torulomata with cryptococcal meningitis.

The patient, a housekeeper aged 57, was admitted to the Maida Vale Hospital under the care of Mr. Valentine Logue on July 26, 1957.

She was a poor witness and, although unable to remember the details of the onset of her illness, she said that for several months there had been an aching pain in the lumbar region which was at first severe but had recently improved and was now situated between the shoulders. About two weeks before admission she suddenly developed a persistent occipital headache which radiated downwards over the neck and forwards to the frontal region; it was made worse by bending down and by lying on her back. She also noticed that she felt giddy, and that objects were jumping in front of her eyes; her eyesight had recently deteriorated, particularly in the left eye. About one week before admission she noticed that her arms had become weak, and she finally took to her bed. Since the onset of her illness she had lost 3 st. in weight.

On examination she was well orientated but her memory was defective. She was not able to perform the serial seven test. There was neck stiffness with pain and limitation of neck flexion and the occiput was tender to percussion. Visual acuity on both sides was diminished to counting fingers only. The optic discs were considerably swollen with venous engorgement and there were hæmorrhages and exudates in both fundi. There was left-sided ptosis. The pupils were normal in appearance: both reacted briskly to accommodation but sluggishly to light. There was nystagmus in both eyes on upward gaze and nystagmus of the left eye on looking to the right. She was unable to abduct the right eye but the other external ocular movements were normal. Both corneal reflexes were absent but sensory and motor functions of the trigeminal nerve were otherwise normal. Facial movements were poor and there was a right lower facial weakness. Hearing was defective in the left ear; she could hear a whispered voice at two feet. Weber's test was not referred, however, and bone conduction was better than air conduction on both sides. Tone was decreased in both arms and there was weakness of the left upper limb, more marked distally. Posture of the outstretched hands was poorly maintained on the left and there was inco-ordination on performing the finger-nose test; the left was worse than the right. There was marked trunk ataxia. Both lower limbs were grossly hypotonic with marked proximal weakness. The tendon reflexes and the abdominal responses were absent. The left plantar response was flexor, the right extensor. There was no loss of sensation except to vibration; this was not felt up to the right knee nor up to the left ankle.

Her temperature was normal and apart from patches of "thrush" on the inside of both cheeks and a smooth shiny tongue there were no other abnormalities.

In view of the gross papillœdema, bilateral cerebellar signs, more marked on the left, and the right extensor plantar response, a clinical diagnosis of posterior fossa tumour was made: because of the defective hearing on the left an acoustic neuroma on that side was suggested. The history of a sudden onset of occipital headache was compatible with a diagnosis of subarachnoid hæmorrhage and a posteriorly situated aneurysm or angioma was also considered.

Investigations revealed a hæmoglobin of 16·6 grammes per 100 ml. (112 per cent), a white cell count of 13,200 per c.mm. of which 91 per cent were polymorphs, and an

erythrocyte sedimentation rate of 3 mm. in one hour. The serum proteins were 6·9 grammes per 100 ml. and electrophoresis revealed a decreased gamma globulin. X-ray of the chest showed an opacity in the right upper lobe suggestive of a neoplasm and x-ray of the skull revealed erosion of the posterior clinoid processes indicative of raised intracranial pressure; the left antrum was opaque. Ventriculography carried out on the day of admission disclosed a slightly dilated ventricular system. The ventricular C.S.F. was under greatly increased pressure and was turbid, containing numerous flaky particles which rendered a cell count impossible. The protein content was 12 mg. per 100 ml., the Lange curve was normal and culture was sterile. In order to exclude a subarachnoid hæmorrhage a lumbar puncture was carried out; the C.S.F. was clear, contained 3 cells per c.mm. and 25 mg. of protein per 100 ml.

On July 30 a repeat x-ray of her chest showed that the opacity in the right upper lobe had cavitated (fig. 1). She died suddenly four days after admission, the clinical diagnosis being carcinoma of the lung with cerebral metastases.

*Pathology.*—Post-mortem examination (Dr. F. D. Bosanquet) revealed a cavitating mass, about 3 cm. in diameter, in the upper lobe of the right lung near the hilum: this resembled a necrotic carcinoma, but there was no enlargement of the hilar lymph glands. Both lung bases were collapsed and congested. Apart from the brain all other organs appeared normal.

The leptomeninges over the whole surface of the brain were thickened distending the sulci, an appearance which was thought to be due to carcinomatous meningitis. There were two nodules, about 3 mm. in diameter, in the white matter of the left parietal lobe. Even at this stage the clinical diagnosis was considered to be correct and it was not until the microscopical examination that the true aetiology was discovered.

*Microscopy.—Lungs.* The necrotic lesion in the right lung consists of a mass of cryptococci together with fibrin and red blood corpuscles. Although there are occasional aggregates of lymphocytes, there is a notable absence of plasma cells and polymorphs. Surrounding this there is very vascular granulation tissue containing many cryptococci, macrophages, fibroblasts, and giant cells; cryptococci are seen in the cytoplasm of the giant cells. The lung tissue around this main lesion is collapsed and oedematous and there is bronchopneumonia at both bases.

*Spleen.* In a routine section of the spleen cryptococci are identified with difficulty using hæmatoxylin and eosin. With PAS, however, the spleen is found to be studded with microscopic foci. No abnormality was found in the other organs apart from the brain.

*Brain.* The leptomeninges are markedly infiltrated and distended by many cryptococci and by faintly eosinophilic amorphous material in which the organisms are embedded. The cellular reaction to the infection is remarkably slight and, when present, consists of perivascular patches of lymphocytes or giant cells in the cytoplasm of which the organisms can be found. The meningeal thickening is well demonstrated by Nissl's stain in which the sulci, widened by the red-staining meninges, are thrown into sharp relief against the pale cerebral substance (fig. 4). The perivascular spaces are also distended and the organisms are found within them, penetrating deep into the brain substance (fig. 10). Cutting such dilated V.R. spaces transversely results in the "soap bubble" appearance described by previous authors. The actual brain substance is normal with the exception of the left parietal lobe in which one of the two tiny torulomata seen at post-mortem has fallen out leaving a clean cavity which is surrounded by normal brain; there is no wall, no cellular reaction and no oedema (fig. 4). The remaining toruloma is a well-circumscribed granulomatous lesion showing dense strands of fibrous connective tissue interspersed with large numbers

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of cryptococci. Except at the periphery, where there are some lymphocytes and giant cells, there is a marked lack of inflammatory response. There is, however, a moderate glial reaction more marked in the grey matter than the white (the toruloma lies at the junction of grey and white matter).

The stained films of the cerebrospinal fluid taken during life were re-examined and only after prolonged search were occasional organisms found.

(3) *J. A. McE.*

*Summary.*—A male, aged 41, three months' headaches: no cause found. Chest X-ray revealed opacity in the right middle lobe; mass in right lung resected, *C. neoformans* found in lesion. No C.N.S. signs but C.S.F. found to be abnormal though organisms not isolated. Died in coma, with meningeal irritation, five weeks after lung resected. Post-mortem showed cryptococcal meningitis.

The patient, a man aged 41 years, was admitted to the National Temperance Hospital on 24.7.55 under the care of Miss Doreen Nightingale. Five days later he was transferred to University College Hospital. He was an Australian who had lived in England for one year and had been well until April 1955, when he developed severe headaches. He denied any cough, anorexia, or weight loss. He had travelled widely in the Middle and Far East and an X-ray of his chest taken in Australia one year before his illness was reported to be normal.

Examination on admission to the National Temperance Hospital revealed no abnormal physical signs except a few glands in the right axilla. Investigations: Hæmoglobin 13·3 grammes per 100 ml. (90 per cent), white blood cells 6,600 per c.mm., polymorphs 69 per cent; lymphocytes 22 per cent, E.S.R. 13 mm. in one hour. X-ray of his chest revealed a mass in the right hilar region (fig. 2) and tomography of this area showed that it was in the anterior part of the middle lobe. Bronchoscopy was negative but as the mass was thought to be either a neoplasm or an hydatid cyst he was transferred to University College Hospital for thoracotomy which Miss Nightingale performed on August 4, 1955. At operation the right middle lobe and a subsegment of the right upper lobe were removed; post-operative convalescence was uneventful except for a low-grade pyrexia which had been present for a few days before operation.

Examination of the surgical specimen showed that the lung tissue of the right middle lobe had been replaced by gelatinous loculi surrounded by firm creamy white tissue. The gelatinous area measured 2·5 × 2·5 × 1·5 cm. and involved the overlying pleura which had also been removed. The larger bronchioles and blood vessels appeared normal and there were no enlarged lymph glands.

Histological examination was carried out by Professor Sir Roy Cameron who reported that the central gelatinous areas were composed of *C. neoformans* surrounded by lymphocytes and fibroblasts with a few macrophages and giant cells, some of which contained cryptococci.

Because of the known predilection of this organism for the central nervous system, and in spite of the absence of abnormal neurological signs, a lumbar puncture was performed on August 15. The C.S.F. pressure was 80 mm.; there were 90 lymphocytes and 70 red blood cells per c.mm.; the protein content was 500 mg. per 100 ml., the chlorides 660 mg. per 100 ml. and the sugar only 13 mg. per 100 ml. The Lange curve was strongly "paretic" (5555532100) and the W.R. was negative. No organisms were found in smears, and cultures were sterile both after three and twenty-one days. On August 28 a course of intravenous 2-hydroxystilbamidine

0·25 grammes daily was begun; this was continued for only three days since he developed headaches, nausea, vomiting and became increasingly drowsy.

By September 2 he was comatose and had developed neck rigidity. Lumbar puncture revealed a pressure of 80 mm. and a xanthochromic fluid. The C.S.F. contained 600 mg. protein per 100 ml., there were 40 cells per c.mm., sugar was absent and tests for globulin were positive. No organisms were seen with indian ink preparations.

He was given a course of parenteral sulphadiazine (1·5 grammes six-hourly) and penicillin (500,000 u. six-hourly) for one week but he remained in semicoma with persistent neck rigidity.

On September 10, following an attempt to pass a Ryle's tube, he developed spasm of the vocal cords. Although he responded to sucking out the larynx and to the administration of oxygen, he developed another attack of spasm and died shortly afterwards.

*Pathology.*—At post-mortem examination (Dr. R. A. B. Drury and Mr. D. B. Griffiths) a well-healed thoractomy scar was found over the right side in line with the fifth rib; on the pleural surface was a smooth oval gelatinous swelling 2·5 × 1 × 1 cm.

The *lungs* were normal except for oedema and the absent right middle lobe. The hilar glands were not enlarged. *Heart:* There was a small gelatinous nodule 2–3 mm. in diameter over the right atrium but no other abnormality.

*Brain:* The brain was congested and several small gelatinous nodules resembling very pale, translucent tubercles were seen over the base. No nodules were found over the cerebrum but there was gelatinous exudate over a few areas of the spinal cord.

*Microscopy.—Heart:* The nodule under the pericardium covering the right atrium consists of a cavity around the edges of which are cryptococci embedded in the interstices of connective tissue. There is a very scanty infiltrate of plasma cells, macrophages, lymphocytes and fibroblasts. The cardiac muscle and endocardium are otherwise normal.

*Lungs:* There are non-specific inflammatory changes with foreign body reaction at the lobectomy site but no sign of cryptococcal infection. The nodule on the scar in the parietal pleura is a hæmatoma. Apart from the central nervous system the other organs are normal.

*Meninges:* The meninges are thickened due to an infiltrate of plasma cells, lymphocytes, macrophages and giant cells. Cryptococci are seen in small numbers, usually in aggregates, each organism surrounded by its own small cavity. There are frequent instances of giant cells engulfing cryptococci (fig. 8). The perivascular spaces are filled with lymphocytes and plasma cells.

*Choroid plexus:* This is honeycombed by a network of small cavities filled with cryptococci. Solitary organisms can be seen each surrounded by a minute cyst; groups of organisms are seen in composite cysts with fine communicating septa. There is a cellular reaction which is patchy and consists predominantly of plasma cells (fig. 9) though lymphocytes, macrophages and giant cells are also present.

*Cerebellum:* The cerebellar cortex is normal but the choroid plexus of the fourth ventricle shows the same changes as elsewhere. With hæmatoxylin and eosin staining no abnormality is noted in the cerebrum; special methods, however, reveal solitary cryptococci in the brain substance. In spite of the presence of organisms well within the cerebrum there is no reaction to the infection.

## Discussion

*Cryptococcus neoformans*, like other pathogenic fungi such as *Actinomyces bovis*, is found as a commensal organism in the mouths of healthy



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subjects. Subpleural granulomata containing cryptococci have been discovered in patients dying of unrelated diseases and this suggests that the initial infection, as with tuberculosis, may be overcome and the organisms encased in fibrous tissue, which breaks down when general resistance is lowered. It seems likely that a lowering of general resistance is the reason for the well-known association of torulosis with Hodgkin's disease and other reticuloses. Since *C. neoformans* is widely distributed in nature, the variable geographical incidence may be explained by the existence of strains of differing virulence as suggested by Greenfield *et al.* (1938). In spite of its wide distribution in nature *C. neoformans* seldom attacks man and when it does it shows a marked affinity for the central nervous system (C.N.S.) where it may take the form of a localized granuloma or a diffuse meningitis. An estimate of 80 per cent has been given for the incidence of C.N.S. involvement in torulosis (Carton and Mount, 1951) but since there may be a number of individuals in good health who have tiny, quiescent pulmonary torulomata (Littman and Zimmerman, 1956) this percentage can be only approximate.

The lung is the usual portal of entry for the organism and all our 3 cases had pulmonary lesions. The site of these lesions was that which would be expected from inhalation of the organism in the recumbent position. Thus, in Case 1 a subpleural nodule was found at autopsy in in the apical segment of the right lower lobe; in Case 2 there was a mass in the right upper lobe near the hilum, and in Case 3 in the right middle lobe. In Cases 1 and 2 the presenting symptoms were neurological and not respiratory; indeed in Case 1 the sub-pleural nodule found at autopsy measured only 3 mm. in diameter and was too small to be seen on the chest radiograph. Case 3, however, presented with pulmonary symptoms and changes were found in the C.S.F. before there were any signs referable to the central nervous system.

The onset of the disease is insidious and the length of history is usually measured in months but varies from weeks (as in Case 1) to years. Neck stiffness and a positive Kernig's sign were present in all cases and are typical of meningitis. Tuberculous meningitis has the same insidious onset and is often the diagnosis made, particularly when there is a pulmonary lesion. Infection with the tubercle bacillus is commoner than with cryptococcus, tends to affect a younger age group and often occurs with a positive family history (case to case infection of torulosis has not yet been reported). The Mantoux test is occasionally helpful in distinguishing between the two conditions and cavitation of the pulmonary lesion is rare in cryptococcosis.

Pyogenic meningitis may be distinguished by finding the causative organism; lymphocytic meningitis has a shorter history and a more benign course; carcinomatous meningitis provides some diagnostic difficulty but there is usually an indication of the primary lesion, and

neoplastic cells may be found in the C.S.F.; sarcoidosis may be distinguished by the markedly raised E.S.R., abnormal serum proteins and positive Kveim test; in neurosyphilis there is usually a positive W.R. in either blood or C.S.F. In cryptococcal infection the degree of fever, rise in sedimentation rate and peripheral white cell count—all of which are usually slight—contrast markedly with the poor condition of the patient; these findings may be related to the fungal nature of the infecting organisms.

The other common diagnosis made in this condition is that of an intracranial neoplasm. It may be extremely difficult to distinguish a toruloma from other space-occupying lesions; cerebral surgical procedures have been carried out on 25 per cent of cases reported in the literature because of a pre-operative diagnosis of either intracranial tumour, cerebral abscess or subdural hæmatoma (Carton and Mount, 1951). Because of the evidence of raised intracranial pressure in our Cases 1 and 2, intracranial tumour had to be excluded and venticulography was carried out—in both cases with negative results.

In view of the rarity of torulosis the diagnosis will be made only if it is borne in mind particularly in cases of subacute meningitis or cerebral tumour. The most useful investigation is examination of the C.S.F. and the accompanying table gives a synopsis of the C.S.F. findings in our cases.

LABORATORY FINDINGS

| | *Case* 1 | | | *Case* 2 | | *Case* 3 | |
|---|---|---|---|---|---|---|---|
| *Cerebrospinal fluid* | *Lumbar* | *Ventricular* 1 | 2 | *Ventricular* | *Lumbar* | *Lumbar* 1 | 2 |
| Pressure mm.$H_2O$ | >300 | — | — | Raised | — | 80 | 80 |
| Appearance | Clear | Clear | Turbid | Turbid | Clear | — | — |
| Cells per c.mm. | 4 | 2 | 26 | — | 3 | 90 | 40 |
| Protein mg. per 100 ml. | 80 | 50 | — | 12 | 25 | 500 | 600 |
| Sugar mg. per 100 ml. .. | — | 80 | 64 | — | — | 13 | 0 |
| Chlorides mg. per 100 ml. as NaCl | — | 700 | 660 | — | — | 660 | — |
| Lange .. | 5443210000 | 0000000000 | 0000000000 | 0000000000 | 0000000000 | 5555532100 | — |
| Wassermann reaction .. | Neg. .. | — | — | Neg. | — | Neg. | — |
| Organisms .. | Neg. | + | + | Neg. | + | Neg. | Neg. |
| Blood: | | | | | | | |
| W.B.C. per c.mm. .. | | 7,000 | | 13,200 | | 6,600 | |
| E.S.R. mm. in 1 hour.. | | 11 | | 3 | | 13 | |

— Indicates "not recorded." + organisms were found.

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It must be emphasized, however, that the C.S.F. may be normal, a poverty of inflammatory response being one of the remarkable features of this disease. The association of a paretic type of Lange curve with a negative blood Wassermann reaction in a clear C.S.F., as seen in the lumbar fluids of Cases 1 and 3, should lead the clinician to consider the possibility of torulosis since this combination is present in few conditions, of which disseminated sclerosis, carcinomatous meningitis and some forms of encephalitis are the most noteworthy. In suspected cases it is essential to search for organisms in wet films of the centrifuged deposit prepared with nigrosin or indian ink. Cultures should also be put up on Sabouraud's medium both at room temperature and at 37° C., but it must be remembered that there may be no growth for several days or even weeks. Indeed, in our third patient, who was known to be suffering from the disease, the organism was neither cultured nor seen in smears in spite of repeated attempts.

The appearance of the organism varies greatly depending on the preparation. Presumably the least distorted appearance is that to be found in unstained wet preparations such as are illustrated by Reeves *et al.* (1941). Here the organism is seen to consist of two parts: a central body with a highly refractile double-contoured surface membrane surrounded by a very thick, smoothly outlined capsule (figs. 11 and 12). Although it has been described by Littman and Zimmerman and others as spherical it is probably disc-shaped. This is suggested by the fact that it has a side view, in which some of the organisms are seen to be cigar-shaped or crescentic, and by the contrast it makes with corpora amylacea which are known to be spherical. When one of the latter is cut 5 or 6 $\mu$ thick, an homogenous evenly stained disc results whereas a cryptococcus stains more deeply around the edge than it does in the centre. The organisms vary in size from 1 $\mu$ to 18 $\mu$ and the smaller ones stain less deeply. With PAS the capsule remains unstained or occasionally that part of it adjacent to the cell body takes up the stain evenly. With cresyl violet and toluidine blue the capsule stains metachromatically, in a pattern of radiating lines or "spikes" (fig. 13). This appearance suggests that the surface only of the capsule has been stained and is thrown into folds which, when seen edge on, show up as this fine network of radiating lines.

In tissue we have found the PAS technique, toluidine blue and Nissl's stains to be the most useful: with all three the organisms are stained red in contrast to their immediate surroundings. Klatzo and Geisler (1958) have described a method of using buffered cresyl violet and crossed Nicol prisms when examining tissue for the presence of cryptococci; the highly refractile organisms are readily seen, the cell bodies appearing red and the capsular "spikes" yellow and green (fig. 14). The appearance of *C. neoformans* in unstained wet preparations is similar to that of a poached egg; this apparently fanciful discription is nevertheless useful since the

behaviour of the coalescing capsules (figs. 12 and 15) bears a distinct resemblance to that of egg albumen; its consistence is likely to be important since the resistance of the organism to therapy may be due to the presence of the capsule.

The pathological findings in our 3 cases were typical of the condition though there are some unusual features. Thus Case 1 had considerable degeneration of anterior horn cells, and atrophy of the posterior roots secondary to involvement of the posterior root ganglia by the organism.

Case 2 had a lung lesion with cavitation which is unusual in torulosis. There was involvement also of the spleen, though not of any other organ. This was presumably due to blood-borne invasion since the spleen was the site of very many minute foci. The only other foci which may have been hæmatogenous in origin were the tiny torulomata in the right parietal lobe: they may, however, have begun as a direct extension from a perivascular space into neighbouring cerebral tissue.

Both Cases 1 and 2 showed evidence of inadequate response to the invading organism: a normal temperature, a normal E.S.R., minimal pleocytosis in the lumbar C.S.F., little tissue cellular response and in one patient a low gamma globulin. These findings are not necessarily typical of mycotic infection, and it has been postulated that failure of immunological response increases the susceptibility of certain individuals to such infection.

Case 3 differed from the other two in showing signs of reaction to the fungus with marked C.S.F changes and a predominantly plasma-cell infiltrate. The small isolated toruloma in the heart was an unusual finding. It is noteworthy that this patient was an Australian who came to Britain a year before his fatal illness. Since torulosis is much commoner in Australia than in Britain it is probable that he was infected more than a year before his symptoms appeared and that during that year he developed the granuloma of his lung.

Single lesions in the lungs have been removed surgically with success but the danger of spread to the C.N.S. remains. Involvement of the central nervous system with cryptococci is usually fatal within six months from the first symptoms although remissions lasting a much longer period have been reported.

Torulosis is a serious therapeutic challenge for the organism is resistant to the commonly used antibiotics. Several antifungal agents have recently been introduced and, while none of these has yet been shown to be consistently effective, reports of successful treatment have now appeared in the literature. Appelbaum and Shrokalkos (1957) have recorded in one case the apparently successful use of intravenous Amphotericin B, the course of therapy lasting for approximately seven weeks. The organism disappeared from the C.S.F. and the patient subsequently became free from symptoms. Fitzpatrick, Rubin and Poser (1958) reported three

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cases of cryptococcal meningitis treated with a slow intravenous drip of Amphotericin B. The dose was increased to 1 mgm./Kg. body weight given on alternate days. They found that the organism was killed *in vitro* by a concentration of 1 μg./ml. of Amphotericin B and that with their regimen adequate blood levels persisted for eighteen hours. One of these 3 patients showed no evidence of infection nine months after the beginning of treatment. Rubin and Furcolow (1958) reported more fully 10 patients with cryptococcal meningitis who had been treated with intravenous Amphotericin B. They gave the drug by intravenous drip dissolving 1 mgm./Kg. body weight in 1 litre of 5 per cent glucose and water, the total doses varying from 1·4 to 3·7 grams. 8 of these 10 patients were alive two to fourteen months later with consistent sterility of the C.S.F. in 7 of the survivors. Although they emphasized that "the normal course of cryptococcal meningitis is characterized by exacerbations and remissions and, therefore, evaluation of therapy is difficult", they concluded that "Amphotericin B seems to be the most promising agent available in the treatment of cryptococcal meningitis". Anderson (1958) in a short review mentioned two cases of torulosis which, when treated with Amphotericin B, showed definite clinical improvement. (Amphotericin B is now available for therapeutic administration in this country.)

Cryptococcal infection is characterized by minimal exudate and fibrosis so that once an effective therapeutic agent is found distorting scar tissue is unlikely to be a sequel as it is, for example, in tuberculosis.

Freeman in his exhaustive monograph, written just over a quarter of a century ago, concluded that "Torula infection of the nervous system has invariably proved fatal . . . The outlook for treatment of the condition is at present without a redeeming feature." It seems that at last there are reasons for adopting a more optimistic view.

## Summary

(1) 3 cases of torulosis of the central nervous system occurring in Britain are reported, the diagnosis being made during life in 2 patients.

(2) The symptomatology, morbid anatomy and differential diagnosis are discussed, and some of the characteristics of the organism (*Cryptococcus neoformans*) producing the disease are considered.

(3) Although all 3 cases were fatal, recent work with a newly introduced antifungal drug, Amphotericin B, suggests that early diagnosis and treatment may now prove rewarding.

It is a pleasure to thank Dr. Denis Williams for his permission to publish Case 1 and for his encouragement. For permission to publish Cases 2 and 3 we would like to thank Mr. Valentine Logue and Miss Doreen Nightingale respectively. The pathological investigations in

PLATE LXXIX

FIG. 1.—Chest X-ray of Case 2 showing cavitating mass in right lung.

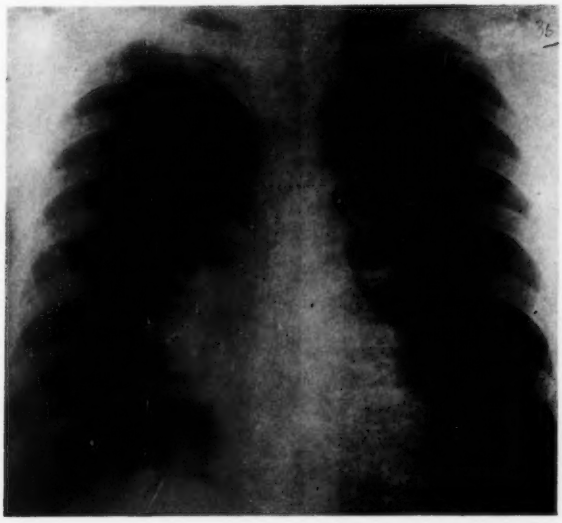

FIG. 2.—Chest X-ray of Case 3 to show right hilar mass.

*To illustrate article by F. Clifford Rose, Helen C. Grant and A. L. Jeanes.*

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FIG. 3.—Horizontal section of brain in Case 1 showing gelatinous thickening of meninges. A dilated Virchow-Robin space cut transversely can be seen in the white matter on the left.

FIG. 4.—Low-power photograph of brain of Case 2 showing toruloma (*below*) and sharply demarcated cavity left by toruloma (*above*) which has fallen out during the preparation.

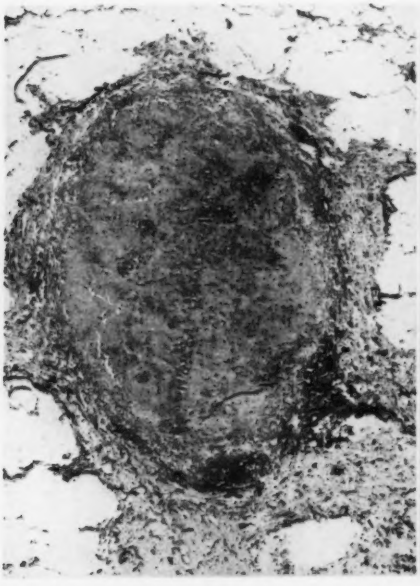

FIG. 5.—Small subpleural nodule found in Case 1. Fibrous tissue with occasional cryptococci (black dots) in the centre. PAS. ×33.

FIG. 6 (*Case* 1).—Showing dilated V.R. spaces cut transversely; the black dots are cryptococci. PAS. ×33.

*To illustrate article by F. Clifford Rose, Helen C. Grant and A. L. Jeanes.*

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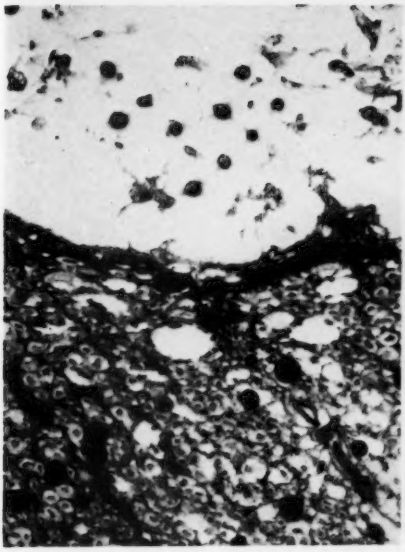

FIG. 7 (*Case* 1).—Meninges containing smaller and less dense cryptococci (upper half) contrasting with spinal cord containing larger and denser corpora amylacea (lower half). PAS. ×140.

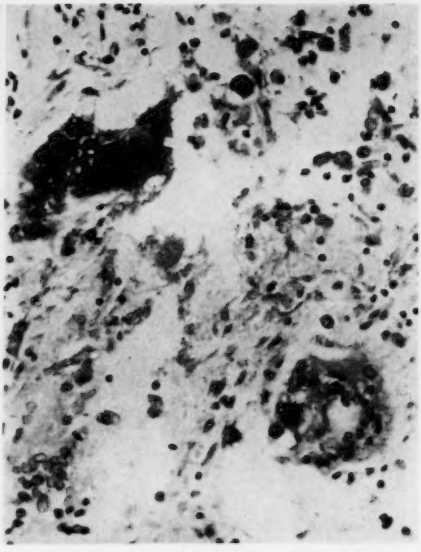

FIG. 8 (*Case* 3).—Giant cells in meninges. Top left and bottom right: organisms being engulfed. Two macrophages are seen filled with granular débris from cryptococci. Toluidine blue. ×280.

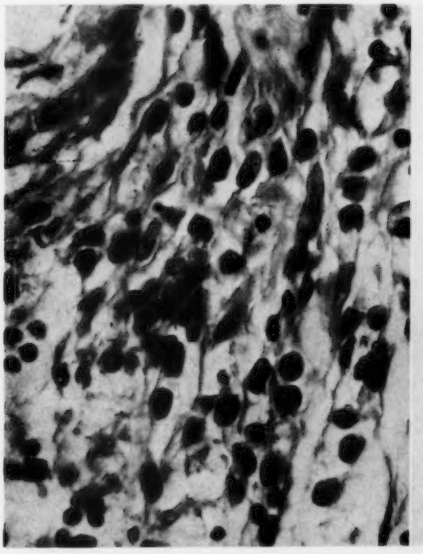

FIG. 9 (*Case* 3).—Infiltrate of plasma cells in choroid plexus. H. & E. ×280.

FIG. 10 (*Case* 2).—Organisms and lymphocytes distending a V.R. space and following it deep into brain substance. H. & E. ×70.

*To illustrate article by F. Clifford Rose, Helen C. Grant and A. L. Jeanes.*

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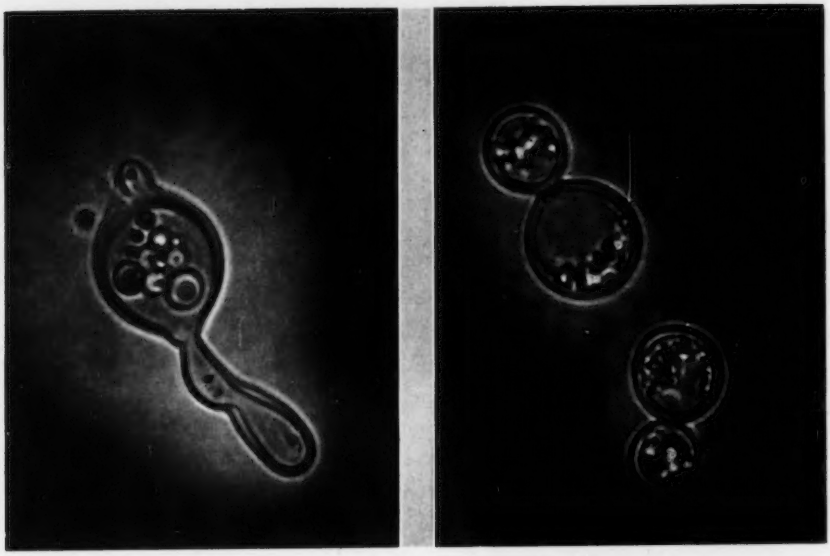

FIG. 11. FIG. 12.

FIGS. 11 and 12.—Nigrosin preparations of *C. neoformans* isolated from Case 1. × 1,200.

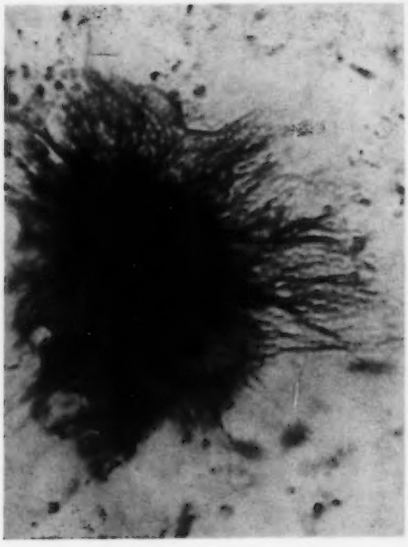

FIG. 13.—High power view of *C. neoformans* in tissue showing radiating spikes ofcapsule. Toluidine blue. × 1,000.

FIG. 14.—*C. neoformans* stained with buffered cresyl violet and examined under polarized light. × 280.

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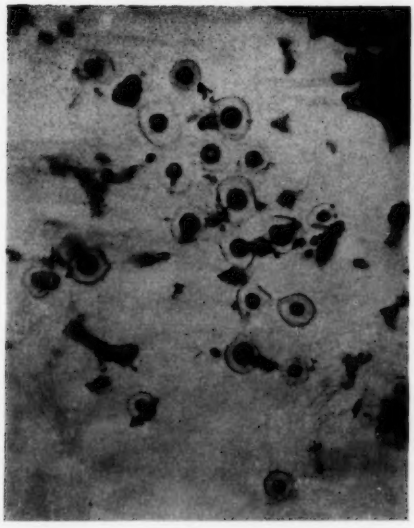

FIG. 15.—Undistorted appearance of *C. neoformans* as seen in stained section Choroid plexus may be seen in top right hand corner. H. & E. × 280.

FIG. 16.—*C. neoformans* isolated from ventricular C.S.F. of Case 1 cultured on Sabouraud's maltose-agar at room temperature for four days. It shows a zone of inhibition produced by Amphotericin B. (100 $\mu$g. in central trough.)

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Case 3 were carried out at University College Hospital; in the Department of Clinical Pathology under Professor Maizels and in the Department of Morbid Anatomy under Professor Sir Roy Cameron.

We are very grateful to Professor W. Blackwood, Professor J. N. Cumings and Dr. W. H. McMenemey for their helpful criticism.

For the illustrations we are indebted to Mr. J. A. Mills, Mr. A. H. Prickett and Mr. G. Cox. E. R. Squibb and Sons Ltd. kindly provided supplies of Amphotericin B for *in vitro* sensitivity studies.

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# ON FAMILIAL ATAXIA, NEURAL AMYOTROPHY, AND THEIR ASSOCIATION WITH PROGRESSIVE EXTERNAL OPHTHALMOPLEGIA[1] [2]

BY

JAMES STEPHENS, MARY L. HOOVER AND JOHN DENST

THAT there is a close relationship between Friedreich's ataxia and the neural type of atrophy described by Charcot and Marie, and by Tooth has been known for many years. There are, however, few published reports on this association. Spiller (1910) described two cases of Friedreich's ataxia, in one of which, where there was wasting of the forearms and marked wasting below the knees, autopsy was performed. In the other, atrophy of the interossei and muscles of the thenar and hypothenar eminences was prominent, with symmetrical wasting of the calves. Spiller commented, "It is noteworthy that in both the cases of Friedreich's ataxia I report in this paper, the atrophy was confined to the peripheral part of the limbs and resembled closely that occurring in neural muscular atrophy." Greenfield (1911) described an isolated case with features of both diseases and there have been further reports by Gallotti (1928), van Bogaert and Moreau (1939–40), Ross (1942), Roth (1948) and Pappworth and O'Mahoney (1954). Recently Shepherd (1955) has described this combination in association with mental disturbances of a schizophrenic nature while Hierons (1956) investigated a family remarkable for the longevity and intellectual achievements of its members.

The family described in the present paper (fig. 10) is of interest in that not only did several members suffer from a combination of spinal ataxia and neural amyotrophy, but they developed a progressive external ophthalmoplegia. Four members of the same generation showed this association; 19 members of subsequent generations had intermediate forms of the disease. We have shown that the ophthalmoplegia was due to a myopathy in the one case where post-mortem examination was performed, and that, in all probability, it was closely related genetically to the

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[2]Presented at the Tenth Annual Meeting of the Canadian Neurological Society, Toronto, Ontario, June 12, 1958.

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central nervous system disorder. In addition, we report details of the spinal cord findings in view of the rarity of pathological examination in cases of combined Friedreich's ataxia and Charcot-Marie-Tooth disease.

The mother of this large family (I, 2) was alive and well at the age of 77. There were no abnormal physical signs on neurological examination. She had two living brothers who were not available and they, according to her information, had no disability. Her husband had died without any signs of nervous disorder but his two brothers had spent their last days in a mental hospital; nothing further could be ascertained about them.

## Case Reports

*Case II* (3).—F. F., propositus—This 49-year-old man had slowly become unsteady since about the age of 15; the condition had progressed until his early twenties when he first had difficulty with his ocular movements, but the family denied any significant change in the last twenty years. On examination, he was pleasant and co-operative albeit a little befuddled. The pupils were small but equal, and reacted poorly to light; the fundi were quite normal. There was marked bilateral ptosis with compensatory wrinkling of the forehead. Elevation of the eyes was not possible. There was 15 degrees of movement to both right and left, but depression was not impaired. The cranial nerves otherwise showed no abnormality. Considerable symmetrical wasting of the thenar and hypothenar muscles, and of the lower third of the forearms, was present. The arms were hypotonic, and weak only in the wasted groups of muscles. The legs were similarly hypotonic without any localized muscle atrophy or loss of power. Each foot had a very high arch and there was some clawing of the toes. Co-ordination in the arms was significantly impaired in that there was a terminal action tremor, more marked on the right than on the left, and rapidly alternating movements were clumsily performed. Tapping was slow and irregular. There was considerable ataxia of the legs. All tendon reflexes were absent; the plantar responses were indefinite. Light touch was impaired on the fingers and not appreciated below the knee on either side. There was hypalgesia of a similar distribution. The ability to discriminate two points was impaired to 1·25 cm. in the fingers of both hands, though sense of passive movement was normal here but severely impaired at the toes. Vibration sense was absent at the ankles and knees and impaired at both wrists. Walking was performed on a wide base with some steppage. He was easily displaced in any direction when standing. There was no kyphoscoliosis. This patient subsequently died of a carcinoma of the bronchus. The findings in the nervous system are the basis of the present pathological report.

*Case II* (4).—J. F., aged 47, the brother of the first case, had been severely disabled for more than twenty years. His disease had commenced before the age of 20 and the initial disequilibration had led to frequent arrests for drunkenness. He was surly and unco-operative and probably of no more than dull normal intelligence. Examination showed similar findings to those in the first case. There was marked ptosis with wrinkling of the forehead, complete inability to look upwards, and less than 10 degrees of movement to either right, left or downwards. The cranial nerves were otherwise intact and there was no dysarthria. There was profound wasting of all the small muscles of the hands and of the lower third of the forearms with a sharp, horizontal upper level. The position of the outstretched hands was irregularly maintained and persistent piano-playing movements of the fingers were present. Weakness was proportional to the wasting. The legs were wasted to the lower third

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of the thigh with appropriate weakness; there was bilateral pes cavus with hammer toes. All limbs were hypotonic. The arms and legs were grossly ataxic and his reeling, high stepping gait indicated both sensory and cerebellar disturbances. Absence of all tendon reflexes was associated with brisk extensor responses to plantar stimulation. There was peripheral hypæsthesia and hypalgesia to the level of the wrists and to the mid-third of the calves. Vibration was not appreciated at the ankles or knees and was but poorly so at the wrists. There was gross impairment of position sense in both fingers and toes and inability to recognize two points at more than 2 cm. over the tips of the fingers. There was no scoliosis.

*Case II* (8).—M. W. This 37-year-old lady, sister of the above two, had been unsteady since about the age of 21. The difficulty had been very slowly progressive. Examination showed slight bilateral ptosis. There was some impairment of upward gaze; lateral gaze was limited to 30 degrees in either direction but downward gaze was unaffected. The cranial nerves were otherwise intact. The position of the outstretched hands was well maintained. Tone and power were normal and there was no wasting. The feet had high arches without definite pes cavus. The appearance and strength of the legs were normal. There was no inco-ordination of the arms and slight ataxia on the heel-knee-shin test was largely corrected by vision. All deep tendon reflexes were absent. The plantar responses were flexor. Sensations of touch and pain were normal throughout. There were occasional mistakes in sense of position of the fingers; there was marked impairment at the toes. She could identify two points at 0·5 cm. on the fingers of the right hand and 0·75 cm. on the left. There was slight impairment of vibration sense at ankles and wrists. At rest, there was swaying of her trunk; she fell when her eyes were closed; her gait was wide-based and steppage in character. There was a slight mid-thoracic scoliosis with the convexity to the right.

*Case II* (9).—M. F. M., aged 33, the youngest member of this generation, first noticed staggering when 19 years of age. The condition had slowly progressed. Bilateral ptosis was evident on examination. Her gaze was limited to 10 degrees upward and 20 degrees to either side. There was full movement downwards; convergence, however, was severely impaired. There was no dysarthria. The thenar eminences were flattened. The position of the outstretched hands was well maintained. The legs, of normal tone, were weak in movements of dorsiflexion, inversion and eversion of the ankles. No tendon reflexes were elicited. Superficial abdominal reflexes were retained and the plantar responses were flexor. Moderate difficulty in repeated tapping movements and rapidly alternating movements was demonstrated in both arms, affecting more the left than the right. Her legs were moderately ataxic. She walked on a wide base, swaying from side to side. Sensations of pain and touch were normally appreciated throughout. Position sense was impaired at all fingers and grossly so at the toes. Vibration was absent at the ankles and knees and only appreciated normally at the clavicles. In the mid-dorsal region there was a slight scoliosis with the convexity to the right.

### Intermediate Forms

*Case III* (1).—Male, aged 35, high-arched feet with claw toes. No other abnormalities.

*Case III* (7).—Female, aged 10. The biceps and supinator reflexes were absent; the triceps present only on reinforcement. There was limitation of motion of both external recti, more on the left.

*Case III* (9).—Female, aged 25, high-arched feet, claw toes. No other abnormality.

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*Case III* (11).—Female, aged 19. Moderate symmetrical thenar atrophy. No other disturbances.

*Case III* (14).—Male, aged 17. Moderate degree of pes cavus and claw toes. Biceps and supinator reflexes absent; triceps present on reinforcement. No other signs.

*Cases III* (15) *and III* (16).—Identical female twins, aged 14. Both showed absent biceps and supinator reflexes; triceps and patellar present only on reinforcement. Rather high arches with some clawing of the toes. Atrophy of muscles of the lower third of forearms with symmetrical thenar atrophy.

*Case III* (18).—Male, aged 22, high-arched feet, slight symmetrical thenar atrophy.

*Case III* (19).—Male, aged 21, high-arched feet, symmetrical thenar atrophy with wasting of the lower third of the leg on either side.

*Case III* (21).—Female, aged 18. Slight thenar atrophy; no other signs.

*Case III* (23).—Female, aged 11, high-arched feet. Biceps and supinator reflexes absent; triceps present on reinforcement. No other signs.

*Case III* (24).—Female, aged 8. Biceps and supinator reflexes absent; patellar and triceps reflexes present only on reinforcement; no other signs.

*Case III* (25).—Male, aged 20. Slight bilateral ptosis with limitation of motion of external recti, more on the left.

*Case IV* (1).—Male, aged 15. Biceps and supinator reflexes just present on reinforcement; others normal.

*Case IV* (2).—Male, aged 14. Biceps and supinator reflexes just present on reinforcement; others normal.

*Case IV* (3).—Male, aged 12. Biceps and supinator reflexes just present on reinforcement; others normal.

*Case IV* (4).—Male, aged 10. Biceps and supinator reflexes just present on reinforcement; others normal.

*Case IV* (8).—Male, aged 11. Biceps and supinator reflexes just present on reinforcement; others normal.

*Case IV* (9).—Female, aged 8. Biceps and supinator reflexes just present on reinforcement; others normal.

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*Case II* (3).—The cause of death was a post-operative intrathoracic hæmorrhage. The bronchial tumour was an undifferentiated carcinoma which had not metastasized. After arterial embalming, the brain weighed 1,310 grammes and was grossly normal. Microscopically there were no abnormalities of the cerebral cortex, cerebellum, pons or medulla.

*Mid-brain.*—Normal numbers of nerve cells with intact nuclei and Nissl substance were present in the nuclei of the third and fourth cranial nerves and of Edinger-Westphal (fig. 8). The emerging fibres of the oculomotor nerve appeared to be normally myelinated.

*Oculomotor nerve.*—The axis cylinders and myelin sheaths of the nerve fibres were intact; the perineurium and endoneurium were unaltered (fig. 7).

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*External ocular muscles.*—The levator palpebræ superioris, superior oblique, and the superior, lateral, and medial rectus muscles were removed from the right orbit. There was diffuse atrophy of the three recti muscles with an increase of mature endomysial collagen. Hypertrophic myofibres were intermingled with atrophic and normal-sized ones in most fields (figs. 2 and 3). The atrophic fibres measured from 8 to 12 microns in diameter, and many were even smaller. Most of the large fibres varied from 20 to 35 microns, but a few were as large as 56 microns. A prominent feature in cross sections was the absence of atrophy and fibrosis in the approximate centre of the belly of the muscles; here the fibres tended to be especially hypertrophic. Longitudinal and cross striations were usually distinct, but many dystrophic fibres showed partial or total disintegration of the contractile substance. Frayed myofibrils often radiated into abundant peripheral sarcoplasm (fig. 4). Occasional large central vacuoles were present. There was an increase in sarcolemmal nuclei at the periphery of the fibres, and many fibres contained one or more central nuclei (fig. 5). There were a few short rows of hypolemmal nuclei. The fibrous matrix contained an abundance of reticulum. Infiltration of the muscles with adipose tissue was moderate. Many small intramuscular nerves appeared to be normal. The superior oblique muscle, in contrast to the recti, was hypertrophic throughout with many myofibres measuring up to 63 microns in diameter (fig. 6).

*Spinal cord.*—Demyelination of the posterior columns extended through the entire length of the cord and was particularly advanced in the columns of Goll (fig. 9). In the upper one-half of the cord a narrow subpial zone of the lateral columns in the region of the dorsal spinocerebellar tracts was also depleted of myelin. The motor tracts were normally myelinated. There was severe fibrillary gliosis and marked diminution of axis cylinders in the posterior columns. Clarke's columns were devoid of nerve cells and participated in the glial scarring. The anterior horns in the cervical region were shrunken due to marked loss of nerve cells. Such a loss was less prominent in the anterior horns and intermediolateral grey columns of the thoracic cord. Normal numbers of motor nerve cells were present in the lumbar region. The spinal nerve roots were normal except for rare swelling and vacuolization of the myelin in the dorsal fibres.

*Peroneal and femoral nerves.*—Focal areas of swelling and fragmentation were present on the axis cylinders of the peroneal nerve and the great majority of fibres were demyelinated. In the femoral nerve, many of the fibres were devoid of myelin, and there was an increase of collagen between the narrow fibres.

*Peripheral muscles.*—The pectoralis major and diaphragm were normal. In isolated myofibres in the head of the peroneal muscle there was a diffuse proliferation of sarcolemmal nuclei; a few fibres were atrophic,

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and in some of these, the contractile substance was coagulated and fragmented. Permission was not obtained for examination of muscles from the distal portions of the limbs.

## Discussion

It is well known that hereditary nervous diseases frequently have an identical course within the same family but vary greatly in different families. Cobb (1954) has criticized the frequent attempts of authors to describe new diseases without pathological data and has emphasized that in hereditary disease the genotype may be constant, whereas the phenotype may vary greatly, according to developmental and environmental influences. It is not considered that a detailed discussion of the precise eponymous classification of this unique family would be profitable. It is clear that these cases exhibited features traditionally associated with both Friedreich's ataxia and Charcot-Marie-Tooth disease and in this respect resemble those already reported in the literature. Since, according to Greenfield (1954), post-mortem examinations have been made in only two cases of combined spinal ataxia and neural amyotrophy (Spiller, 1910; Gareiso and Pedace, 1948), it is of interest to compare the present findings with those previously reported. Spiller found degeneration of the lumbar and sacral posterior roots and of the posterior columns. In the cervical region the degeneration in the column of Goll was more marked than in the column of Burdach. In the lumbar and sacral regions the posterior horns contained fewer fibres than normal and in the mid-thoracic region, replacing Clarke's column, there was an area of dense gliosis. Despite the degeneration, a large number of axis cylinders remained intact in the posterior columns. In both lumbosacral and cervical regions there was slight degeneration of the crossed pyramidal tracts and the direct cerebellar tracts. Throughout, there was no loss of anterior horn cells or abnormality of the anterior roots. Sections of peripheral nerves showed severe degeneration. In the case described by Gareiso and Pedace (1948) there was degeneration of the posterior columns and Clarke's columns. There was marked loss of cells in both anterior and posterior horns and in the lower cranial nerve nuclei. The pyramidal tracts were normal throughout. Thus, a finding common to the two reported cases and ours is the degeneration of the posterior columns and Clarke's columns. Degeneration of pyramidal tracts was found only by Spiller and was slight. The peripheral muscular wasting seems to be of varied cause. In Spiller's case it was clearly due to peripheral nerve degeneration whereas in that of Gareiso and Pedace there was profound depletion of anterior horn cells. In our case, the wasting of the legs was not accompanied by loss of lumbar cells but by degeneration of the femoral and peroneal nerves, yet in the arms, where the wasting was similar, there was considerable loss of anterior horn cells

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in the cervical region. Unfortunately, we were not able to examine the ulnar and median nerves.

The intermediate forms of these diseases were described independently and almost simultaneously by three groups of authors. Symonds and Shaw (1926), discussing familial pes cavus and absent tendon reflexes, related the condition to peroneal muscular atrophy and observed that there might be some wasting of the calf and the small muscles of the hand. Rombold and Riley (1926) considered the syndrome to be an abortive form of Friedreich's disease. Roussy and Lévy (1926) maintained that their cases of hereditary areflexic dystasia constituted a separate disease entity. They stressed the constant characteristics of the illness as disturbances of station and gait with generalized loss of tendon reflexes and clubfoot. In addition to these essential signs, there were certain others: a slight clumsiness of the hands, rarely atrophy of the muscles of the palms, and a tendency toward extension of the great toe. No anatomical verification was obtained and subsequent reports (Spillane, 1940; Lusso, 1952) have made their view untenable.

The progressive ophthalmoplegia in the present cases merits further consideration. Some degree of peripheral muscular wasting is a frequent occurrence in cases of Friedreich's ataxia. This wasting has most often involved the small muscles of the hand (Hodge, 1897; Bäumlin, 1901); has occasionally occurred in the proximal musculature (Jendrássik, 1902); and has been assumed to reflect changes in the anterior horn cells (Schut, 1954). A loss of motor nerve cells in the lower cranial nerve nuclei has been reported (Schut and Haymaker, 1951); this was marked in the hypoglossal nuclei in the case described by Gareiso and Pedace (1948) where there was atrophy and fasciculation of the tongue. It has been assumed that such a nuclear lesion was responsible for the ocular muscle weakness present in some cases of familial ataxia. This association was a prominent feature in the family described by Sanger Brown (1892) and was again noted by Londe (1895), Mathieu and Bertrand (1929), and Rosenhagen (1943). In Sjögren's (1943) extensive study of familial ataxia in Sweden, of 139 cases, ptosis was noted in 5 and oculomotor paresis in 9. The concept of progressive nuclear ophthalmoplegia has been severely criticized by Kiloh and Nevin (1951). They point out that involvement of the external ocular muscles in classical muscular dystrophy, though rare, has been reported, and describe 5 cases of progressive external ophthalmoplegia in 3 of which there was associated wasting of shoulder girdle muscles or sternomastoids. In 2, satisfactory biopsy of an external ocular muscle was obtained showing great variation in the size of the fibres with numerous proliferated sarcolemmal nuclei. Throughout were many bundles of normal nerve fibres. In an extensive review of the literature they found 3 cases (Fuchs, 1890; Silex, 1897; Vollaro, 1933) in which biopsy of the eye muscles had been performed and interpreted as

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showing dystrophic changes. In addition, a report by Sandifer (1946) of a biopsy specimen examined by Greenfield clearly demonstrated a dystrophic pattern. From this review and their own findings, Kiloh and Nevin concluded that the concept of primary degeneration of the oculomotor nuclei as a cause of progressive external ophthalmoplegia had no pathological basis, and suggested that cases of so-called progressive "nuclear" ophthalmoplegia were, in fact, examples of ocular myopathy. Because of the small number of muscle fibres in a motor unit in the external ocular muscles, the pattern of atrophy is unusually difficult to interpret and proof as to its myopathic origin must depend on the demonstration of normal oculomotor nuclei and integrity of the nerve bundles. Three cases with post-mortem examination of both oculomotor nuclei and external ocular muscles have been published. That of Jedlowski (1943) lacks detailed description and the only satisfactory accounts are those of Beckett and Netsky (1953) and Schwarz and Liu (1954). The former found the ganglion cells of the nuclei to be normal in number and appearance. The muscle fibres were partially replaced by fatty tissue; the remaining fibres showed focal but widespread increase in sarcolemmal nuclei. In the case of Schwarz and Liu there was profound atrophy of the external ocular muscles with fragmentation of fibres, loss of striations and phagocytosis of disrupted myofibres. In addition to examining the oculomotor nuclei and their emerging fibres, they demonstrated normal axis cylinders and intact motor end-plates between and on degenerating muscle fibres. These findings strongly supported the conclusions of Kiloh and Nevin. In our case, the external ocular muscles showed typical dystrophic changes. The oculomotor nuclei, their emerging fibres and the peripheral nerves were normal. This finding was confirmed by Dr. Jerzy Olszewski to whom we submitted the slides for an independent opinion, and who stated that in the nuclei of the third nerve, "the number of nerve cells does not appear to be reduced, there is no gliosis, the Nissl pattern is usual and the nuclei are vesicular and lightly stained. In particular, I have not seen one single cell that shows any signs of degeneration either in the form of chromatolysis or pyknosis."

It is apparent that in the present family a genetically determined neuropathy and myopathy were associated. Such an association had been postulated by the early clinical observers in this field. Bäumlin (1901) commented on the occurrence of pseudohypertrophy of the shoulder muscles with Friedreich's disease, while Kollarits (1908) concluded that the muscular atrophy occurring in some cases might be dystrophic in nature. Kinnier-Wilson (1940) accepted that all variations between true spinal amyotrophy and muscular dystrophy might occur. However, Mackay (1954) stated, "I have never seen, I believe, the concurrence of a dystrophy and one of these familial neuro-abiotrophies. I do not think,

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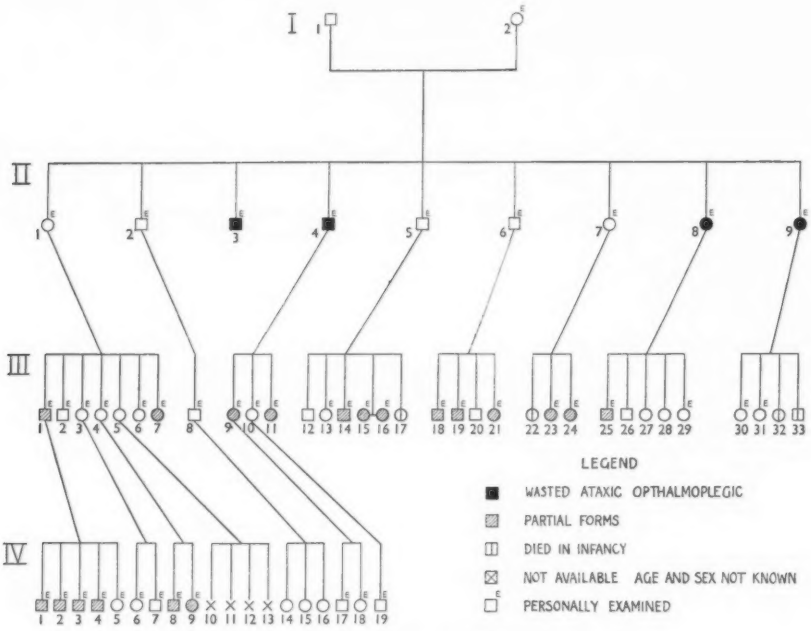


FIG. 10.—Genealogical chart.

therefore, that it is very likely that the genetic defects upon which the two types of disorders are based can be in any way similar or closely related to each other." Stevens (1954) reported the association of familial periodic paralysis, myotonia, progressive amyotrophy and pes cavus in members of a single family, and Ziegler and Rogoff (1956) described a variant of dystrophia myotonica in which there was peripheral sensory loss, pes cavus, scoliosis and ataxia. These observations support the earlier assumptions. In our case, the question may be asked whether the findings are consistent with a single genetic abnormality, or is the observed association merely the accidental combination of two defects? The full genetic analysis of the pattern of inheritance seen in this family is complex and will be considered elsewhere. Our best estimate of the incidence of ophthalmoplegia is 4/9ths. The members with the rest of the defects also comprise 4/9ths of the family. If we assume that the inheritance of these defects is independent, the probability of being afflicted with both is 4/9 x 4/9 or 16/81sts. The chance of being spared from both is (1-4/9) (1-4/9) or 5/9 x 5/9; i.e. 25/81sts. All nine of generation II fall in these two classes of "all" or "none." The probability of 9 people being "all" or "none" can be calculated: (16 + 25)/81

raised to the ninth power, which is about 1 in 500. It seems unwise, therefore, to discard the possibility of a close connexion, if not the identity of the underlying genetic defect, as this pattern is so unlikely to be produced at random.


## Summary

A family is described in which four members of one generation showed features of Friedreich's ataxia and Charcot-Marie-Tooth disease associated with external ophthalmoplegia, and 19 members of subsequent generations had formes frustes of these diseases. Post-mortem examination of one case showed the ophthalmoplegia to be due to a primary ocular myopathy. The spinal cord findings are compared with those in the two previously autopsied cases of combined spinal ataxia and neural amyotrophy. It is concluded that in this family the chance association of a neuropathy and a myopathy is unlikely, and the evidence is consistent with a single genetic abnormality.



## Acknowledgments

We are very grateful to Dr. Jerzy Olszewski of the University of Saskatchewan for examining the oculomotor nuclei, and to Dr. N. Conant Webb, Jr., for advice on the genetic mechanisms.


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FIG. 1.

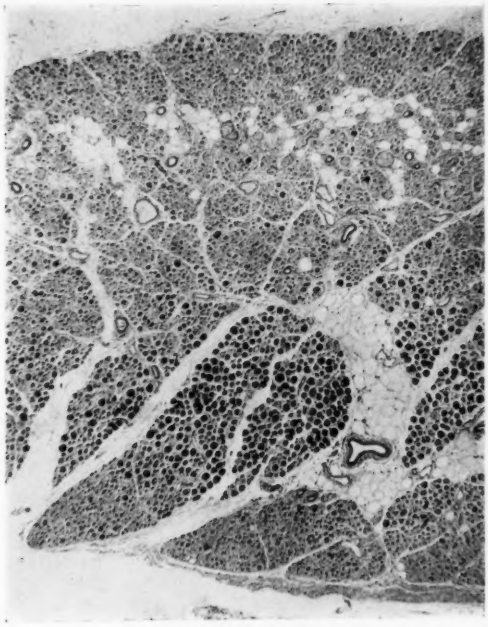

FIG. 2.

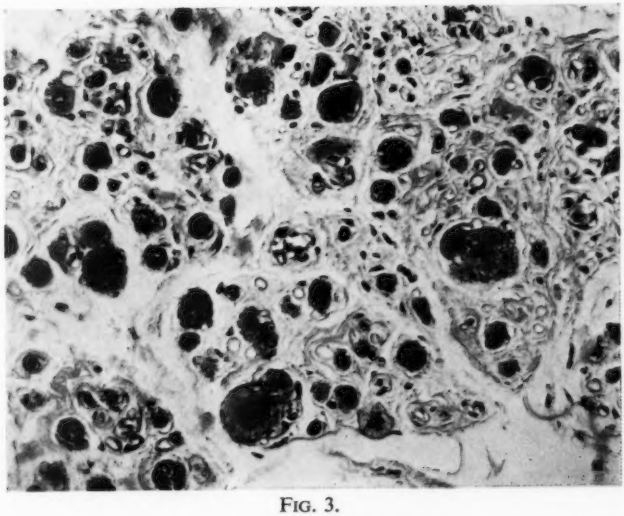

FIG. 3.

FIG. 1.—Gomori tri-chrome × 8. Cross section of lateral rectus showing large fibres in the lower mid-portion of the belly of the muscle.

FIG. 2.—Gomori tri-chrome × 25. Higher power view of the central portion of the muscle in fig. 1.

FIG. 3.—Gomori tri-chrome × 210. Same muscle showing atrophy and hypertrophy of myofibres and abundant connective tissue.

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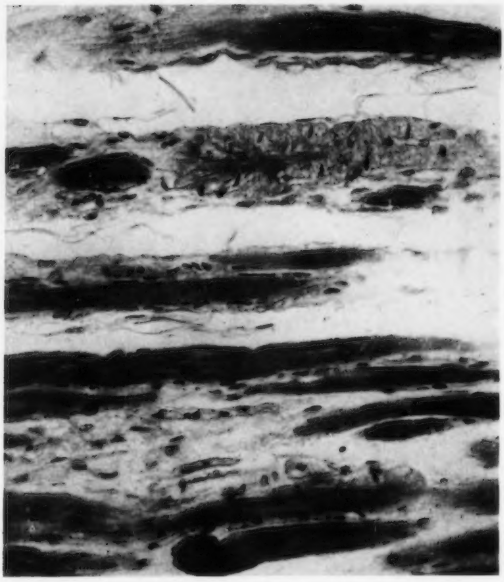

FIG. 4.—Hæmatoxylin-eosin × 210. The central myofibrils in a swollen fibre of the lateral rectus are frayed and radiate into the sarcoplasm.

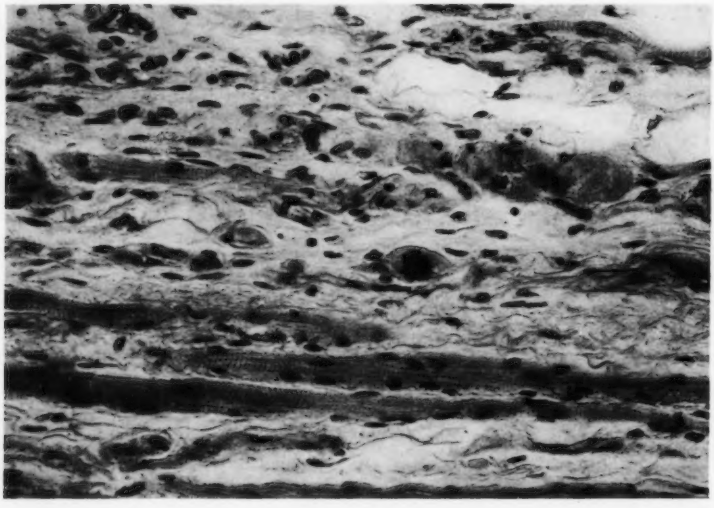

FIG. 5.—Hæmatoxylin-eosin × 300. Medial rectus muscle showing loss of myofibres, and a degenerated fibre with much sarcoplasm and proliferated sarcolemmal nuclei.

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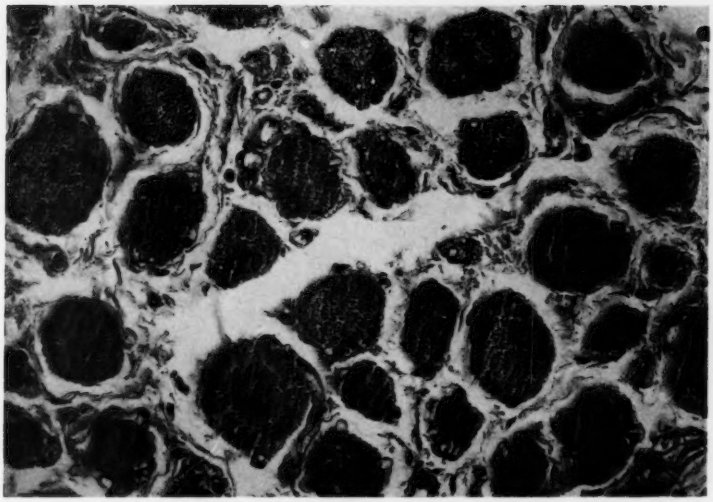

FIG. 6.—Hæmatoxylin-eosin × 300. Superior oblique muscle showing hypertrophy and central nuclei.

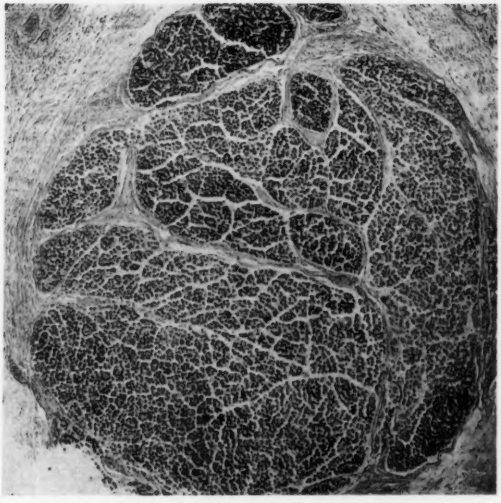

FIG. 7.—Spielmeyer × 50. Normal oculomotor nerve.

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FIG. 8.—Nissl × 30. Nucleus of oculomotor nerve with normal number of cells.

FIG. 9.—Spielmeyer × 7. Demyelination of the posterior columns and of a thin peripheral band in the lateral columns of the spinal cord.

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# DORSAL SPINAL ROOT AFFERENTS TO CLARKE'S COLUMN

BY

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## INTRODUCTION

CLARKE (1851) in his original observations on the "posterior vesicular column," now commonly termed Clarke's column or the nucleus dorsalis of the spinal cord, noted that the nucleus was traversed and surrounded by fibres from the dorsal spinal roots. Bechterew (1887), Takács (1887) and Mott (1888) also observed that dorsal root fibres proceeded to Clarke's column. Ziehen (1899), Collier and Buzzard (1903), Bing (1906), Pass (1933) and many others confirmed these early observations. Ramón y Cajal (1909), Bok (1928), Strong (1936), Laruelle and Reumont (1938), Hogg (1944) and others pointed out that the fibres of Clarke's column consisted of collaterals from the dorsal spinal roots. Pass, Brodal (1954) and others uphold the generally accepted view that the afferents to Clarke's column originate from the lower extremities and the trunk.

The present investigation was begun in 1954 to ascertain how the dorsal spinal roots of the cat project on Clarke's column. Liu (1956) published detailed observations on degeneration in Clarke's column and the lateral cuneate nucleus following section of dorsal spinal roots in cats. Our observations are not in complete agreement with Liu's and we have some additional observations to present.

## MATERIAL AND METHODS

19 adult cats weighing between 1·5 and 4·1 kg. were used. Anæsthesia was produced by nembutal—40 mg. per kg. body-weight—injected intraperitoneally. In 15 of these cats following laminectomy a single dorsal spinal root was cut centrally to the dorsal spinal root ganglion and in 4 cats two or three adjacent dorsal spinal roots were similarily cut. The spinal cord within its membranes was covered with muscle and then 100,000 I.U. of crystalline penicillin were spread over the muscle. The cut roots lay between the sixth cervical and fourth sacral inclusively. The cats were killed between two and forty-three days following the operation by administration of ether. They were then exsanguinated by opening the heart. The cut root was marked and the spinal cord removed and fixed in 5 per cent formol-saline for at least seven days. The segment corresponding to the cut root and the

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segments caudal and rostral to it were examined histologically. Transverse sections were impregnated with silver using mainly the technique of Nauta and Gygax (1954) and in addition in some sections that of Nauta and Ryan (1952) was also used.

Transverse sections of the spinal cord of normal cats stained by toluidine blue were already available to demonstrate the structure and extent of Clarke's column. Similarily transverse and longitudinal sections of the spinal cord of normal cats impregnated with silver according to Glees method (1946) were available for comparison with those of the experimental animals.

## Results

*General.*—Clarke's column is found to lie behind and lateral to the central canal and within lamina VII of the nerve-cell groups described by Rexed (1952, 1954) and extends from the third or fourth lumbar segment to the third and sometimes to the second or first thoracic segments. It is constantly found at the third lumbar and third thoracic segments. Caudally the nucleus extends to the mid-line but rostrally has a more lateral location. Its caudal end is sharply demarcated. The nerve cells in Clarke's column are most numerous in the upper lumbar and lower thoracic segments; each segment in these situations has about the same number of nerve cells. In the most rostral segments, where Clarke's column occurs the nerve cells are scanty and lie singly or in small groups, and the column is less easily defined. The ventral margin of Clarke's column does not extend ventral to the mid-point of the central canal.

The nerve cells of Clarke's column are medium to large in size, the largest being about the size of the larger motor cells of the ventral horn. They are rounded more frequently than star-shaped and in sections only one or two large processes can be demonstrated. Smaller spindle-shaped nerve cells also occur. The larger cells have large granules of Nissl substance and the nucleus lies frequently at the periphery of the cell. A perinuclear zone containing little or no Nissl substance is very common.

When a dorsal root is cut the degenerating axones proceeding to Clarke's column are strictly unilateral. The degeneration issues from the dorsal white column on the same side as the cut root, passes in small bundles to Clarke's column and spreads out within it. These degenerating fibres of Clarke's column are collaterals of the degenerating fibres of the dorsal white column (Ramón y Cajal and others) and enter Clarke's column by way of the whole breadth of the grey matter lying immediately dorsal to Clarke's column.

Table I gives details of the spinal nerve roots, which were cut and the extent and location of the degeneration which subsequently occurred within Clarke's column.

When the dorsal roots caudal to and including the second thoracic were cut degeneration was found in each case within Clarke's column.

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TABLE I

| (1) *Root cut* | (2) *Survival period* | (3) *Segments with degeneration in CC** | (4) *No. of segments with degeneration in CC* | (5) *Sections with degeneration confined to dorsomedial or medial part of CC* | (6) *Sections with degeneration confined to lateral part of CC* | (7) *Sections with degeneration throughout CC* | (8) *Extent of degeneration rostral to the cut root* | (9) *Extent of degeneration caudal to the cut root* |
|---|---|---|---|---|---|---|---|---|
| S 4–3 | 6 days | L 3–T 13 | 4 | T 13 | | L 3–L 1 | 10 segments | |
| S 1 | 2 „ | L 3–T 13 | 4 | L 1–T 13 | | L 3–L 2 | 8 „ | |
| L 7 | 7 „ | L 3–T 11 | 6 | T 13–T 11 | L 3 | L 2–L 1 | 9 „ | |
| L 6 | 6 „ | L 3–T 13 | 4 | T 13 | L 3 | L 2–L 1 | 6 „ | |
| L 5 | 43 „ | L 3–T 12 | 5 | T 12 | L 3–L 2 | L 1–T 13 | 6 „ | |
| L 3 | 5 „ | L 3–T 10 | 7 | | L 3–T 11 | T 10 | 6 „ | |
| L 1 | 6 „ | L 1–T 8 | 7 | T 8 | L 1–T 10 | T 9 | 6 „ | 0 segments |
| T 13 | 6 „ | T 13–T 7 | 7 | T 7 | T 13 | T 12–T 8 | 6 „ | 0 „ |
| T 8 | 6 „ | T 10–T 5 | 6 | | T 10–T 8 | T 7–T 5 | 3 „ | 2 „ |
| T 7 | 5 „ | T 9–T 4 | 6 | | T 9–T 8 | T 7–T 4 | 3 „ | 2 „ |
| T 6 | 6 „ | T 7–T 2 | 6 | | T 7–T 5 | T 4–T 2 | 3 „ | 1 „ |
| T 5 | 6 „ | T 6–T 3 | 4 | | T 6 | T 5–T 3 | 2 „ | 1 „ |
| T 2 | 5 „ | T 3–T 2 | 2 | | | T 3–T 2 | 0 „ | 1 „ |
| T 1 | 6 „ | No degen. | | | | | | |
| T 1–C 7 | 7 „ | „ „ | | | | | | |
| C 8 | 5 „ | „ „ | | | | | | |
| C 8–C 6 | 4 „ | „ „ | | | | | | |
| C 8–C 6 | 5 „ | „ „ | | | | | | |
| C 7 | 6 „ | „ „ | | | | | | |

* CC = Clarke's column.

When the dorsal roots rostral to the second thoracic segment were cut no degeneration was found in Clarke's column.

When a single dorsal root was cut degenerating nerve fibres from it were found to project on to Clarke's column in several segments of the spinal cord, in some instances in as many as seven segments e.g. when the third or first lumbar or thirteenth thoracic dorsal roots were cut (Table I, columns 1 and 4).

Degeneration was found in Clarke's column two to ten segments rostral to the cut sacral, lumbar and thirteenth to fifth thoracic dorsal roots inclusive; it was found in the same segment as the entering root in the case of the cut third lumbar to the second thoracic roots inclusive; and it was found one to two segments caudal to the cut eighth to second thoracic dorsal roots inclusive.

The degenerating fibres from different dorsal roots may project on to Clarke's column of the same segments. The third lumbar dorsal root for instance projects on to the third lumbar to the tenth thoracic segments and the thirteenth thoracic dorsal root projects from the thirteenth to the seventh thoracic segments (Table I, columns 1 and 3). Fibres from both these dorsal roots are found in Clarke's column in the tenth to the thirteenth thoracic segments of the cord.

*Sacral roots.*—When the sacral dorsal roots were cut degeneration was seen throughout the cross section of Clarke's column in four segments of the cord, and in the most rostral segments it was located in the medial or dorsomedial part of Clarke's column.

*Lumbar and thirteenth thoracic roots.*—When the lumbar and the thirteenth thoracic dorsal roots were cut, the caudal extremity of degeneration in Clarke's column lay in its lateral part. The rostral extremity of degeneration, however, lay in the dorsomedial part of Clarke's column. Between the rostral and caudal extremities of degeneration there were one to five segments and here degeneration occurred in the whole cross section of Clarke's column (Table I, columns 1, 6, 7 and 5). When the third lumbar dorsal root was cut the rostral end of degeneration was distributed throughout the cross section of Clarke's column and not confined to its medial or dorsomedial part.

The degeneration in Clarke's column passed from a lateral position in the most caudal extremity of the degeneration to occupy the entire cross section of Clarke's column in more rostral segments. This took place within one to six segments depending upon which root had been cut (Table I, columns 1, 6 and 7).

The most rostral degeneration in Clarke's column occupied a dorsomedial position. In the case of the third lumbar root, however, this was not demonstrated. This shift to a dorsomedial position took place within one to three segments, depending upon which root had been cut (Table I, columns 1, 7 and 5).

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The degeneration in Clarke's column in the third lumbar segment was found in a lateral position after cutting the seventh, sixth, fifth and third lumbar dorsal roots respectively. Degeneration in the lateral part of Clarke's column in the third lumbar segment was most extensive when the seventh lumbar dorsal root was cut. The extent of this laterally situated degeneration steadily diminished on cutting the most rostral dorsal roots up to the third lumbar, and on cutting this the smallest extent of lateral degeneration occurred.

*Eighth to second thoracic roots.*—When the dorsal roots from the eighth to the fifth thoracic segments were cut, the caudal extremity of degeneration in Clarke's column lay in the lateral part of the column, and degenerating fibres were found in the whole cross section of Clarke's column over several segments of the cord. The transition occurred within one to three segments, depending upon which root had been cut (Table I, columns 1, 6 and 7). No segments with degenerating fibres confined to the medial or dorsomedial part of Clarke's column were demonstrated in the rostral extremity of the degeneration.

When the second thoracic dorsal root was cut, degenerating fibres were found in the whole cross section of Clarke's column in the third and second thoracic segments. There were no segments with degeneration only in the lateral or dorsomedial or medial part of Clarke's column.

To illustrate our results details of representative cases are given below.

*Seventh lumbar dorsal root cut* (Cat 201.–10.002). The right seventh lumbar root was cut, and the cat was killed seven days later. In the third lumbar segment massive ipsilateral degeneration was found in sections of Clarke's column, only a medial zone being free from degenerating fibres. Massive degeneration was found throughout the whole cross section of Clarke's column in the second lumbar segment, and also in most of the sections from the first lumbar segment. In some sections of the first lumbar segment the degeneration was confined to the medial zone of Clarke's column and in the thirteenth thoracic segment the degeneration was confined to the dorsomedial half of Clarke's column. In the twelfth thoracic segment massive degeneration occupied a crescentic zone in the dorsomedial part of the column. Some degeneration was seen in the dorsomedial part of the eleventh thoracic segment but none was found in the tenth and the ninth thoracic segments.

*Fifth lumbar dorsal root cut* (Cat 204.–10.005). The left fifth lumbar dorsal root was cut, and the cat was killed forty-three days later. Massive ipsilateral degeneration was found in the lateral quarter of Clarke's column in the third and in the lateral half in the second lumbar segment and throughout its cross section in the first lumbar segment. Less degeneration was seen throughout the cross section of the column in the thirteenth thoracic segment. A crescentic zone showing a moderate degree of degeneration was present in the dorsomedial part of the twelfth

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thoracic segment. No degeneration was seen in the eleventh thoracic segment.

The degenerating fibre bundles from the dorsal white column passed through the grey substance just dorsal to Clarke's column. Where the degeneration lay in the lateral part of the dorsal white column the degenerating fibre bundles to Clarke's column were situated laterally; where the degeneration in the dorsal white columns was more medially situated the degenerating fibres to Clarke's column entered via its medial portion.

*Fifth thoracic dorsal root cut* (Cat 9.–10.115). The left fifth thoracic dorsal root was cut, and the cat was killed six days later. No degeneration in Clarke's column was seen caudal to the sixth thoracic segment; in this segment ipsilateral degeneration of a moderate degree was seen in the lateral part of Clarke's column. More marked degeneration was seen throughout the cross section of Clarke's column in the fifth thoracic segment. A slight degree of degeneration was seen throughout the cross section of Clarke's column in the fourth and third thoracic segments. The second thoracic segment did not present any degeneration.

*Eighth cervical dorsal root cut* (Cat 14.–10.120). The left eighth cervical dorsal root was cut, and the cat was killed five days later. No degeneration was found within Clarke's column at any level of the numerous sections examined from the fifth to the first thoracic segment. However, numerous degenerating fibres were found surrounding Clarke's column in the second to the fifth thoracic segments. The degeneration was lesser in degree in the fifth thoracic than in the more rostral segments.

## Discussion

In accordance with earlier observations on the cat by Pass using the Marchi technique, by Schimert (1939) using the Bielschowsky-Gross technique, and by Liu (1954, 1956) using silver impregnated sections according to Nauta's technique and also by various other workers, our experiments have shown that only ipsilateral collaterals from the posterior roots go to Clarke's column. Szentágothai and Albert (1955) made similar observation in dogs using the silver impregnation technique of Reumont and Lhermitte.

The dorsal spinal roots caudal to the first thoracic segment have a relatively extensive projection on to Clarke's column, a single root projecting on to two to seven segments (Table I, columns 1, 3 and 4). This is in agreement with the observations of Liu, although in our experiments the degeneration observed in Clarke's column extends over fewer segments than was found by Liu.

Ipsilateral degeneration in Clarke's column following section of a dorsal root was seen in the segment corresponding to that root. A similar observation was made in dogs by Rasdolsky (1928) using Lichtgrün-

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Fuchsin B staining and in cats by Pass. Schimert did not find any degeneration in the cat in the segment corresponding to the cut root. He considered that the degeneration in Clarke's column occurring at the same level is due not to section of the root but that it occurred during the laminectomy. Liu, however, cut dorsal spinal roots in cats without performing a laminectomy and he found degeneration in Clarke's column at the same level as the cut root.

Pass, Schimert, Szentágothai and Albert, Liu and others observed degeneration in Clarke's column rostral to the cut dorsal root. Pass after cutting the first sacral and seventh lumbar dorsal roots in a cat found in Marchi preparations that degeneration extended rostrally as far as the first lumbar segment—i.e. six segments rostrally. Using Nauta's technique we found that the degeneration in Clarke's column after cutting the first sacral and the seventh lumbar dorsal roots extended to the thirteenth and eleventh thoracic segments respectively, a greater extent of degeneration than observed by Pass.

Our experiments demonstrate that degenerating fibres occur in Clarke's column in segments caudal to that of the cut dorsal root. Similar observations were made in man by Collier and Buzzard using Marchi preparations and by Rasdolsky and Szentágothai and Albert in dogs. Schimert in his experiments on cats did not find any caudal degeneration in Clarke's column after section of the dorsal roots. But Liu observed degenerating fibres in Clarke's column in the cat caudal to the level of the root section and he found it over a greater number of segments than we did in our experiments.

The generally accepted view is that the cervical and the first thoracic dorsal roots do not project on to Clarke's column. This has been confirmed in the cat by Ranson, Davenport and Doles (1932), Pass (1933), Corbin and Hinsey (1935) and Escolar (1948) using the Marchi technique. Escolar also used sections stained according to the technique of Rasdolsky. Pass cut the sixth and seventh cervical dorsal roots. The other workers cut the upper three or four cervical dorsal roots Schimert after extirpating the sixth and seventh cervical dorsal root ganglia stated that he found in segments rostral to the extirpated ganglia degeneration around "Clarke's column cells" lying in the medial part of the posterior grey column; Clarke's column does not, however, extend into the cervical segments of the spinal cord (Rexed, 1952).

Liu made the original observation that cutting the fifth to the eighth cervical and the first thoracic dorsal roots was followed by the appearance of degenerating fibres in Clarke's column; it appeared in the first two thoracic segments in the case of the fifth cervical, and in five or more thoracic segments in the case of the seventh and eighth cervical and first thoracic roots. We did not find any degeneration in Clarke's column after cutting of the first thoracic and the eighth to the sixth cervical

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dorsal roots inclusive. We did, however, observe numerous degenerating fibres passing around Clarke's column particularly dorsal and lateral to it and some degenerating fibres in the intermedio-medial nucleus lying just ventral or ventromedial to Clarke's column.

Clarke's column is absent in the cervical spinal cord and sometimes in the first and second thoracic segments but its homologue is thought to be the lateral cuneate nucleus of the medulla oblongata; to this nucleus are distributed afferents from the upper extremity, the neck and the upper trunk (Brodal, Liu and others). We have not included any observations on the lateral cuneate nucleus.

Laruelle and Reumont (1938) using Weigert preparations studied birds (chicken and turkey), mammals (rabbit, cat, dog, fox, monkey) and man (the fœtus from the third month till birth, the child each year up to the tenth year and the adult). They found that the more caudal dorsal roots, which pass into the fasciculus gracilis give collateral fibres which are distributed to the most medial groups of nerve cells in Clarke's column; the fibres from the more rostral roots enter the fasciculus cuneatus and give collaterals which are distributed to the lateral groups of nerve cells in Clarke's column.

Szentágothai and Albert in their study of the lumbar region of Clarke's column found after cutting dorsal roots in dogs that the "afferents belonging to the sacral segments are establishing contact with medial Clarke neurons, those from the upper lumbar segments with those situated in the lateral part of the column."

In our experiments the sacral dorsal roots were distributed throughout Clarke's column in its most caudal end but the most rostral fibres were distributed in the medial or dorsomedial part of Clarke's column.

The lumbar dorsal roots and thirteenth thoracic root gave afferents to Clarke's column and in their most caudal distribution they lay in the lateral part of the column and in the dorsomedial part of the column at the most rostral limit of the distribution. In the intervening segments afferents from these roots were distributed throughout the cross section of Clarke's column.

Degenerating fibres emerging from the eighth to the second thoracic dorsal roots inclusively lay in the lateral part of Clarke's column in the caudal distribution of the degeneration and throughout the cross section of Clarke's column in the more rostral segments.

In no instance after sectioning dorsal roots did we observe that the rostral limit of the distribution lay in the dorsomedial or medial part of Clarke's column. This may, however, be due to the fact that some of the fibres project more rostral to the lateral cuneate nucleus, which, as previously mentioned, is considered to receive fibres from the upper part of the trunk, the upper extremity and the neck. Ferraro and Barrera (1935) studying sections from the spinal cord and medulla oblongata of

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rhesus monkeys found that fibres from the lower cervical and high thoracic dorsal roots end in the mediodorsal portion of the lateral cuneate nucleus.

## Summary

Nineteen cats were used to find out how degeneration was distributed in Clarke's column after unilateral section of single and multiple dorsal spinal roots.

(1) When a dorsal root was cut, the degeneration in Clarke's column was ipsilateral.

(2) Degeneration may extend in Clarke's column throughout as many as seven segments after cutting a single dorsal root. Clarke's column in a particular segment of the spinal cord may receive fibres from several dorsal roots, and there is considerable overlapping of these fibres.

(3) After cutting any sacral dorsal root degeneration occurs throughout Clarke's column in the caudal distribution of the degeneration and in the dorsomedial part in the rostral distribution.

After cutting any of the lumbar or the thirteenth thoracic dorsal roots the degeneration seen in Clarke's column lies in the lateral part in the caudal region, in the dorsomedial part in the rostral region, and throughout the column in the intervening segments.

After cutting any of the eighth to the second thoracic dorsal roots the degeneration seen in Clarke's column lies in its lateral part in the caudal distribution and throughout the column in the rostral distribution of the degeneration.

(4) Degenerating fibres were not found in Clarke's column when the first thoracic and the cervical dorsal roots were cut.

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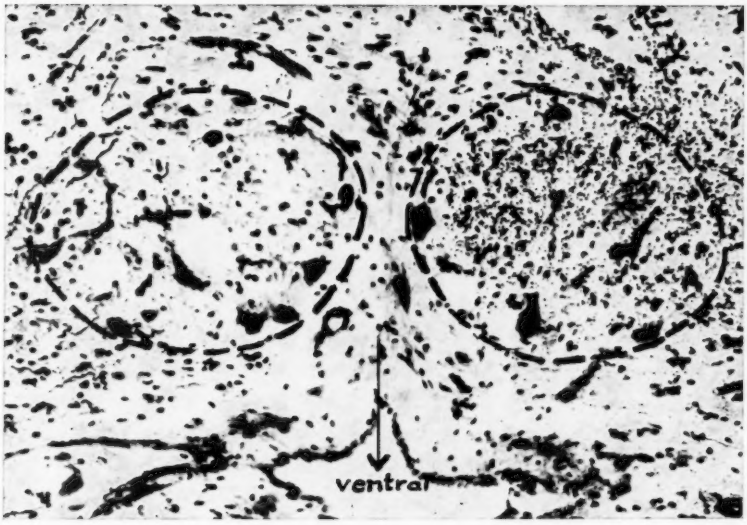


FIG. 1.—A transverse section from the second lumbar segment showing degeneration in Clarke's column on the right only after cutting the first right sacral dorsal root. The Clarke's columns are encircled (×170). (Nauta preparation.)

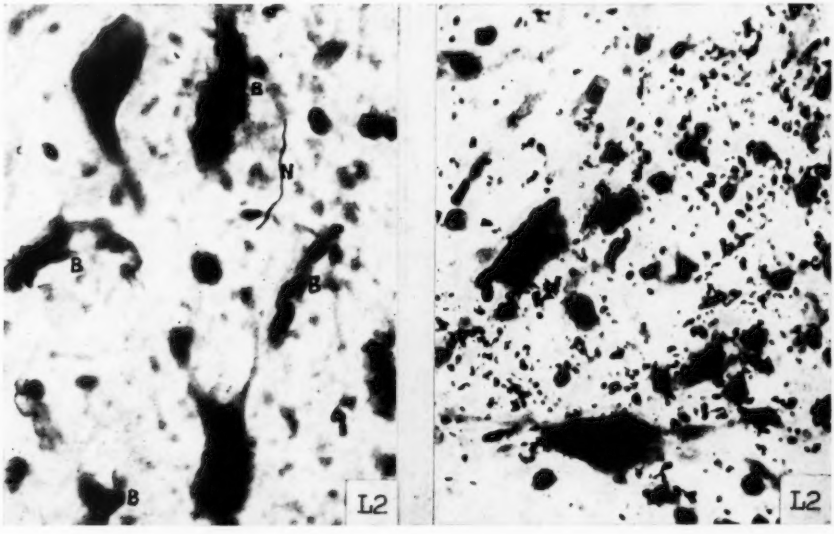


FIG. 2.—A high power view of Clarke's columns from the above second lumbar segment (×600). (Nauta preparation.)

2a.—Clarke's column on the left is free from degeneration. N is a normal nerve fibre and B blood capillaries.

2b.—Clarke's column on the right shows degenerating nerve fibres.

*To illustrate article by Gunnar Grant and Bror Rexed.*

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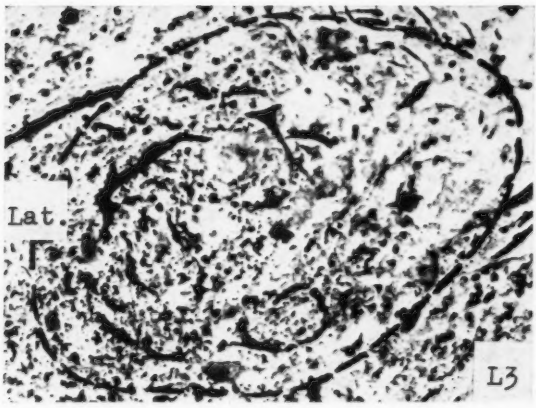


FIG. 3.—Clarke's column—within the interrupted lines—from the left side of the third lumbar segment after cutting the sixth left lumbar dorsal root. The degeneration is confined to the lateral part of the column (×180). (Nauta preparation.)

FIG. 4.

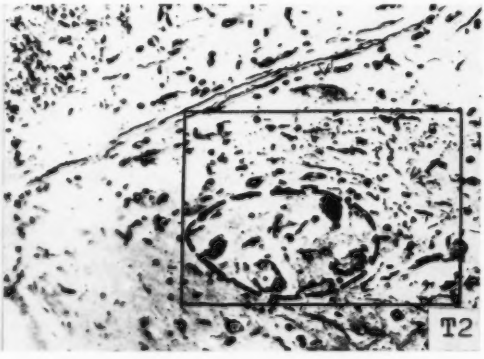


FIG. 5.

FIG. 4.—The eleventh thoracic segment shows degeneration confined to the dorsomedial part, DM, of Clarke's column on the right—within the interrupted lines—after cutting the seventh right lumbar dorsal root (×160). (Nauta preparation.)

FIG. 5.—A transverse section of the left Clarke's column—within the interrupted lines—from the second thoracic segment after cutting the eighth left cervical dorsal root. No degeneration is seen within the column but degeneration is seen within the lined area dorsal and lateral to it (×160). (Nauta preparation.)

*To illustrate article by Gunnar Grant and Bror Rexed.*

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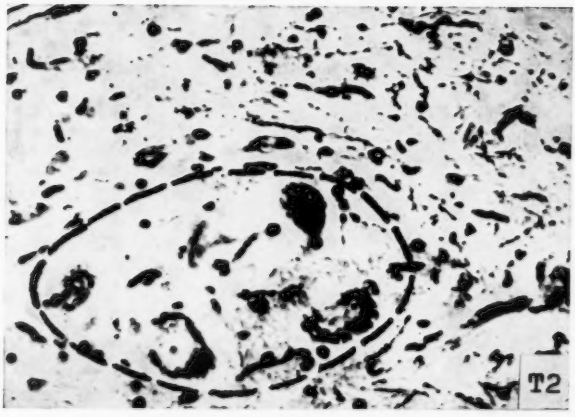


FIG. 5A.—A higher magnification to show details of the degeneration dorsal and lateral to Clarke's column within the lines on 5 (×290). (Nauta preparation.)

*To illustrate article by Gunnar Grant and Bror Rexed*

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# THE FASCICULUS INTERMEDIOLATERALIS OF LOEWENTHAL IN MAN

BY

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## INTRODUCTION

ACCORDING to classical textbooks the ventrolateral funiculus can be divided into three concentric layers: "the lateral limiting layer" (seitliche Grenzschicht), "the intermediate mixed zone" (vordere gemischte Seitenstrang), and "the remaining system of the lateral funiculus" (lateral System der Seitenstrangrest).

Within the intermediate mixed zone a descending system has been frequently described by classical authors, partly overlapped by the spinocerebellar tract and running between other ascending long fibres as well as many short ascending and descending ones (Schiefferdecker in the cat, 1876; Singer in the cat, 1881; Homén in the cat, 1882; Loewenthal in the cat, 1885.) This fibre system is known as the fasciculus intermediolateralis of Loewenthal.

Marchi (1886) identified the system as the cerebellospinal tract. Their opinion is based on their experiments on monkeys and dogs. Biedl (in the cat, 1895) and Friedländer (in the dove, 1898) supported Marchi's view, however, many other authors challenged it. Ferrier and Turner (1894) investigated the degenerations following lesions of the cerebellum of the monkey and could not confirm Marchi's statement. Based on his experiments in monkeys and dogs in which lesions were made in the restiform body, the lateral tegmentum of the medulla, the nucleus of Deiters, and the nuclei of the posterior funiculi, Risien Russell (1897) concluded that not cerebellospinal but reticulospinal and some vestibulospinal fibres partake in the formation of the intermediolateral fascicle. This opinion is in accordance among others with the view of Held (in the cat and the rat 1892) and Tschermak (in the cat 1898). Risien Russell ascribed the misinterpretation that cerebellospinal fibres exist and run partly within the intermediate mixed zone to the coinvolvement of the reticular substance and the vestibular nuclei in the lesions of the restiform body and the cerebellum.

It is generally known that both the localization and the composition

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of fibre systems in the cord differ from level to level. When the intermediolateral fascicle of Loewenthal does consist predominantly of reticulospinal fibres, then in man it is applicable to the cervical cord only, because in man and the monkey in all probability the reticulospinal fibres within the intermediate mixed zone of the ventrolateral funiculus do not proceed caudally to the thoracic levels (Cooper and Sherrington 1940 in the macaque; Foerster and Gagel 1932 in man).

In his later paper, Loewenthal (1892) discussed the property of the intermediolateral fascicle and adhered to the supposition of Singer and Münzer which he referred to in his publication of 1892, that long intersegmental fibres form the constituents of the system. This opinion is substantiated by the findings of Sherrington and Laslett in the dog in 1903.

Summarizing the classical views about this system, it can be said that there are three opinions: it is a cerebellospinal, a reticulospinal, and an intersegmental spinal system.

In the current textbooks (Riley, 1943; Mettler, 1948; Ranson, 1953; Strong and Elwyn, 1953) long descending fibres within the intermediate mixed zone of the ventrolateral funiculus are neither described nor mapped. Even in the recent publication no study is devoted to such fibres.

As previously referred to, it is clear that our knowledge about the fasciculus intermediolateralis of Loewenthal is derived from laboratory animals only, while substantiations for its existence in man are lacking. As stated justifiably by Nathan and Smith (1955) it is misleading and wrong to applicate uncritically findings in laboratory animals to the human central nervous system. Adhering to the opinion that verification of anatomical data acquired in animal experiments is necessary in order to establish a real human neuroanatomy, this paper will present the findings which substantiate the existence of the intermediolateral fascicle of Loewenthal in man.

## Material and Methods

The material consists of 6 human cases of ventrolateral cordotomy and 3 human cases containing either operative lesions or foci of softening.

The study of the fibre degeneration is done with the help of serial cross-sections stained according to the technique of Alzheimer-Mann-Häggqvist (Sie, 1956). Myelinated fibres of all sizes can be distinguished; the axon is stained blue and the myelin-sheath red. Wallerian degenerated fibres can easily be distinguished from eight days on to two months after axonal severance. They are characterized by disappearance of their axons and swelling of their myelin-sheaths, which are filled with catabolic substance staining brilliantly red. Degenerated and normal fibres both can be observed in the same slide and therefore their relation

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as to their site, spreading, sizes, and quantitative proportions can be studied more exactly than in Marchi-stained slides.

## Observations

*Cases I, II, III, IV, V, VI* (H.3364, H.3681, H.3682, H.3863, H.3991, H.4037)

From a number of cases of ventrolateral cordotomy 6 are found to be appropriate for study because the operative lesions involve the ventrolateral funiculus and a part of the ventral funiculus only (photomicrograph 7) and moreover the whole spinal cord is available.

In all case the ventrolateral funiculus is sectioned at the level between T.3 and T.5, nineteen to forty-five days before death.

In all cases similar findings can be noticed, only some difference is observed with regard to the quantity of the fibres degenerated in one case (H.3682). There the section is performed forty-five days ante mortem and a considerable part of the degenerated fibres have disappeared and have been replaced either by compound granular cells or lacunæ. Therefore it is unnecessary to describe each of the identical cases separately and one description will do. Descending degeneration within the ventral funiculus will be mapped in the schemes only and be left out of consideration.

*The descending degeneration.*—Closely adjacent to the lesion the ventrolateral funiculus is totally degenerated, about 1 cm. caudally to the lesion, however, the dorsolateral and the peripheral areas are free of degenerated fibres. Dense degeneration can be seen in the intermediate mixed zone and the juxtagriseal white matter, the former extending ventroperipherally though decreasing in degree (fig. 1). It consists of fibres of all sizes, the thin ones predominating. Over a short distance caudally many degenerated fibres disappear, however a considerable part of axonless degenerated fibres more or less keep their position through some thoracic segments (photomicrographs 10, 11, 12). The intermediate mixed zone in this paper implies about the middle three-fifths of the ventrolateral funiculus.

About 2 segments caudally to the lesion the degeneration rapidly grows diffuse as many thin fibres (up to 3$\mu$) and a part of the thick fibres (up to 8$\mu$) steadily drop out. The normal area in the dorsolateral part gradually becomes broader. However the juxtagriseal white matter still contains scattered degenerated fibres of all sizes, and the ventroperipheral part a few scores of thick degenerated ones (fig. 2). Further caudally many degenerated thick fibres shift ventrally and ventrolaterally. The intermediate mixed zone, though maintaining the larger number of degenerated fibres, loses many of them.

At T.10 a few degenerated thick fibres can be found medially to the ventrolateral sulcus, straying mediocentrally to join the bulk of the

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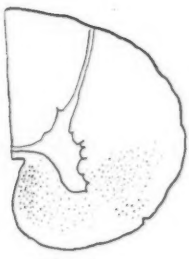

Fig. 1

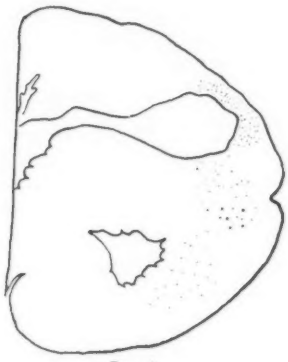

Fig. 4

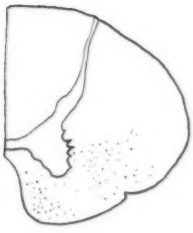

Fig. 2

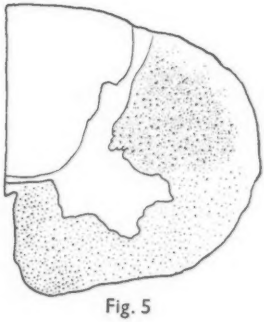

Fig. 5

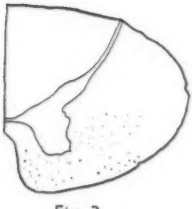

Fig. 3

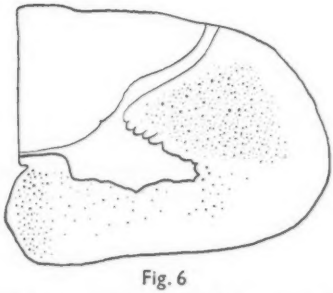

Fig. 6

FIG. 1.—1½ cm. caudally to the high thoracic ventrolateral cordotomy. Cases I–VI.

FIG. 2.—3–4 segments caudally to the high thoracic ventrolateral cordotomy. Cases I–VI.

FIG. 3.—8 segments caudally to the high thoracic ventrolateral cordotomy. Cases I–VI.

FIG. 4.—1 cm. caudally to the caudal extent of the softening focus in Case VII.

FIG. 5.—1 cm. caudally to the hemidestruction at C.3 in Case IX.

FIG. 6.—4 segments caudally to the hemidestruction at C.3 in Case IX.

degeneration consisting of a few scores thick and medium-sized diffusely spread axonless fibres. Along the ventrolateral border of the ventral horn some solitary degenerated fibres can steadily be found (fig. 3). Further caudally a very small number of degenerated fibres are scattered over the ventral part of the intermediate mixed zone. No value can be attributed to degenerated fibres in the grey matter, since the ventral funiculus also contains descending affected fibres, which are distributed to the grey matter. It is unfeasible therefore to determine which part of the grey matter receives the descending degenerated fibres from the ventrolateral funiculus.

In order to examine whether the degenerated fibres are of supraspinal origin two appropriate cases are available.

*Case VII* (H.297)

Due to occlusion of a branch of the posterior inferior cerebellar artery the lateral part of the tegmentum of the medulla together with the lateral funiculus are softened (photomicrograph 8). The corpus restiforme, a part of the reticular substance and the lateral funiculus are involved within the softening.

Descending degeneration beyond the lateral funiculus of the medulla and its adjacency will be left out of consideration.

*The descending degeneration.*—About 1 cm. caudally to the softening degenerated fibres can be found diffusely spread over the ventromedial part of the funiculus lateralis medullæ.

At C.1 a considerable number of degenerated thin fibres are enmeshed in the lateral pyramidal tract. An extremely small number of degenerated thick fibres run diffusely ventrolateral to the area of the lateral pyramidal tract. Along the medial side of the peripheral densely packed normal fibre bundle of the ventrolateral funiculus degenerated medium-sized and thin fibres are found straying ventromedially (fig. 4).

At the caudal level of the first cervical segment a part of the degenerated medium-sized fibres are still present, dispersed over the periphery of the intermediate mixed zone. Since lower parts of the cord are not available they cannot be followed further caudally.

*Case VIII* (H.2653)

The other case identical to the previous one also consists of the brainstem and the first cervical segment only. Because of intractable pain a unilateral cordotomy at low medullary level combined with rhizotomy of the first three posterior roots are carried out one month before death. Almost the whole funiculus lateralis at low medullary level is sectioned together with the adjacent parts of the reticular substance (photomicrograph 9).

The descending degeneration within the ventrolateral funiculus of C.1



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corresponds to that in Case VII, except the small number of degenerated thick fibres ventrolateral to the area of the lateral pyramidal tract which are lacking.

Comparing the degree of fibre degeneration at C.1 of Cases VII and VIII (1½ cm. caudally to the severance) and that at a level 1½ cm. caudally to the ventrolateral cordotomy of the Cases I–VI reveals that in the latter many more degenerated fibres of all sizes can be counted (figs. 4 and 1). Quantitatively the degeneration at 1½ cm. caudally to the medullary section (Case VIII) corresponds to that at 8–12 cm. (8 segments) caudally to the severance of the first 6 cases (figs. 4 and 3). However since the supraspinal severance involves only a small part of the reticular substance it is likely that at C.1 more fibres within the ventrolateral funiculus will come to degeneration, if larger parts of the reticular substance are destroyed. Still it may be suggested that lesions of the reticular formation in a very low medullary level are not followed by descending degeneration within the ventrolateral funiculus passing beyond the cervical cord. At any rate, Cases VII and VIII point to the presence of descending fibres of supraspinal origin within the ventrolateral funiculus.

The next case to be described will provide information to determine the quantity and caudal extent of those fibres.

*Case IX* (H.419)

In this specimen destruction of C.3 caused by a metastatic carcinoma of the thyroid gland is found. The exact outlines of the lesion cannot be determined because of damage affected at autopsy partly due to the extensive softening of the tissue. Study of the fibre degeneration closely rostral and caudal to the damage discloses a hemidestruction of the cord with at the other side a part of the ventrolateral funiculus spared.

At C.4/5 the dorsolateral and the ventrolateral funiculi included the sulcomarginal zone of the ventral funiculus are massively degenerated (fig. 5). At C.7 the peripheral and the juxtagriseal layers of the dorsolateral funiculus are intact. The rest of it still shows a dense degeneration. The larger part of the ventrolateral funiculus is free of degeneration. In a strip parallel to the ventrolateral edge of the ventral horn and separated from it by an intact strip of white matter a small number of degenerated fibres are found. Most of them are medium-sized and they are dispersed among normal fibres (fig. 6).

Passing through the lower parts of the cervical cord they do not demonstrate a noticeable shifting, however, their number decreases gradually. At T.1 they are practically absent.

## Discussion

*I. The results.*—As the results of the severance of the ventrolateral funiculus between T.3 and T.5 a descending degenerated fibre system

can be followed down to the lumbar enlargement. It consists of fibres ranging between 1–8$\mu$ in diameter. They are diffusely spread over the whole ventrolateral funiculus. However, they show a tendency to prevail within the intermediate mixed zone, which comprises the middle three-fifths of the ventrolateral funiculus. Caudally along a distance of 2–3 segments the mass of degenerated fibres loses rapidly many of its thin components and a part of its thick ones. After passing 3–4 segments caudally degenerated fibres decrease in number gradually. When they reach the vicinity of their termination presumably they come to run within the juxtagriseal white matter, for, steadily degenerated fibres of all sizes can be found diffusely along the ventrolateral edge of the ventral horn.

Its long components shift ventrolaterally and ventrally during their descent. At T.10 a few scores of them can be found diffusely scattering over the intermediate mixed zone and a few medial to the ventrolateral sulcus. At lumbar region they are hardly recognizable. Summarizing, it can be said that the fibre system consists predominantly of short fibres terminating at different levels of the cord and that its long constituents proceed down to the lumbar enlargement.

As the result of destruction of the lateral funiculus and the adjacent part of the reticular substance of the medulla a small number of degenerated fibres can be traced to the ventrolateral funiculus. They are certainly fibres of supraspinal origin. According to my study on the human medulla (Sie, 1956) they represent reticulospinal fibres. The question whether they are identical to those descending fibres which come to degenerate after severance at T.3–T.5 can be ruled out, since hemidestruction of C.3 does not cause a descending fibre degeneration within the ventrolateral funiculus which proceeds beyond the first thoracic segment. However, the long reticulospinal ones do partake to a slight extent in the formation of the other fibre system. The presence of crossed corticospinal fibres is not likely because straying corticospinal fibres can be found neither in the ventromedial nor ventrolateral parts of the ventrolateral funiculus.

Based on the above-mentioned findings the conclusion is reached that the diffusely descending long fibres within the intermediate mixed zone of the ventrolateral funiculus arise between C.3 and T.3. It is very likely therefore that they originate predominantly in the cervical enlargement. The fibres with a length up to 3–4 cm. (2 segments) however may arise either from the cervical or thoracic levels.

As previously mentioned the descending fibre system within the intermediate mixed zone of the ventrolateral funiculus is known as the intermediolateral fascicle of Loewenthal. Some authors among which Obersteiner (1901, in man) considered the tract to be identical to the rubrospinal tract (aberrirendes Seitenstrangbündel). In my study (Sie,

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1956, in man) it was stated that the rubrospinal tract in man is rudimentary and the site of its constituents at C.1 is within the dorsolateral area of the ventrolateral funiculus. In Case VII of the present study a small number of degenerated thick fibres were found in that area ventrolateral to the area of the lateral pyramidal tract. In all probability they represent the rubrospinal fibres since its area in the medulla was comprised in the softening (Sie, 1956, in man). Therefore it can be said with certainty that rubrospinal tract fibres do not partake in the formation of the descending fibre system within the intermediate mixed zone of the ventrolateral funiculus.

*II. Evaluation of the Findings.*—Based on findings derived from human cords in which ventrolateral cordotomy has been performed, completed with information from specimens with severance of the lateral funiculus of the medulla and a part of the reticular substance together with a case with a hemidestruction of C.3 a long diffusely descending fibre system within the intermediate mixed zone of the ventrolateral funiculus can be identified. Its constituents originate chiefly in the cervical enlargement, they are distributed to all thoracic levels and the longest ones reach the lumbar enlargement. Moreover many short fibres partaking in the formation of that fibre system constitute intersegmental connexions. In its whole it can be called the descending spinospinal fibre system within the intermediate mixed zone of the ventrolateral funiculus, comprising the intersegmental short descending fibres, the cervicothoracic, the cervicolumbar fibres, together with some reticulothoracic ones. This view is in accordance with Sherrington's and Laslett's opinion (1903, in the dog).

That fibre system has been known as the tract of Loewenthal, however, Schiefferdecker (1876, in the cat) already described it before him. In his thesis Loewenthal (1885, in the cat) described its course only, its origin was not established and with regard to it he was vague. Based on his findings derived from hemicordotomy and cortex ablation cases the conclusion was made that it was not equivalent to the crossed lateral pyramidal tract fibres, however, he did not rule out positively the possibility that corticospinal fibres originating from cortex areas beyond the parts he ablated may form that fibre system. ("Il reste toujours la possibilité que les dites fibres soient en connexion avec les régions corticales qui sont restées intactes dans les expériences que j'ai décrites" (Loewenthal, 1885). Des dégénérations secondaires de la moelle épinière consécutives aux lésions expérimentales médullaires et corticales. Genève, p. 111.) Later in 1892 he adhered to the supposition of Singer and Münzer that intersegmental fibres constitute the system. Up till 1903 the origin of that fibre system is uncertain. It was established only by Sherrington and Laslett (1903 in the dog). They made use of the method which is introduced by Münzer and Wiener in 1895 as referred to by them in their

paper of 1910. Sherrington and Laslett traced the descending degeneration in the cord of dogs in which at two levels parts of the cord were isolated by sectioning the cord at two levels with an interval of 260 days (successive degeneration method). From their experiments they concluded that the descending fibres within the ventrolateral funiculus are both long and short spinospinal fibres, and that they play a role in the long and short reflex mechanism.

With regard to the opinion that the fibre system arises in the cerebellum, Case VII, in which a softening focus involves the caudal part of the restiform body, provides evidence to reject it.

The other view that the fibre system is composed of reticulospinal fibres cannot be fully disregarded. In Cases VII and VIII a part of the reticular substance is concerned in the severance, however, a large part of the reticular substance at the transition of the medulla into the cord is intact. The small number of the degenerated fibres found in those cases may be ascribed to the small destruction of the reticular substance. However, if they do exist in large numbers they must show as such in the case of hemidestruction at C.3 (Case IX). Since the degeneration below the hemidestruction in this Case IX is followable to T.1 only the conclusion is reached that reticulospinal fibres within the ventrolateral funiculus cease at the caudal end of the cervical enlargement. It is possible that some of them reach the higher parts or the thoracic cord. This finding is supported by the investigation of Foerster and Gagel in man (1932). In cases of thoracic ventrolateral cordotomy they could not find retrograde cell degeneration within the reticular substance.

From the above-mentioned findings, it can be said that the reticulospinal fibre system within the ventrolateral funiculus of the human cord is in reality a reticulocervical system and that it together with the cervicothoracic and the cervicolumbar fibres constitute the intermediolateral fascicle of Loewenthal which is very likely one chain-like system within the ventrolateral funiculus.

In the human pathology diffuse sclerosis of the intermediate mixed zone of the ventrolateral funiculus is frequently noticed in cases of amyotrophic lateral sclerosis and primary spastic paraplegia (Charcot, 1878; Gowers, 1892; Risse, 1899; Bertrand and v. Bogaert, 1925). Gowers was of the opinion that the narrow strip-like sclerosis within the inner layer of the ventrolateral funiculus in these diseases is due to degeneration of affected propriospinal neurons. According to Ziehen (1899) the degeneration of the descending fibre system in the intermediate mixed zone of the ventrolateral funiculus is responsible for the hypertonia in amyotrophic lateral sclerosis.

The experimental data and the statements from pathological human cases about the descending short and long spinospinal fibres within the ventrolateral funiculus suggest that also in man they are homologous to

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the reticulospinal fibres of the cervical ventrolateral funiculus and that both fibre systems constitute the interconnexion between propriospinal neurons.


## SUMMARY

A descending spinospinal fibre system within the intermediate mixed zone of the ventrolateral funiculus of the human cord is analysed with the help of 9 cases containing ventrolateral cordotomies, an operative lesion at low medullary level, hemidestruction of the third cervical segment and a softening focus within the lateral part of the tegmentum medullæ.

The investigation is done with the help of the Alzheimer-Mann-Häggqvist method.

It is stated that the descending spinospinal fibre system within the intermediate mixed zone of the ventrolateral funiculus consists of intersegmental, cervicothoracic and cervicolumbar fibres. It is regarded as homologous to the reticulospinal fibres within the intermediate mixed zone of the ventrolateral funiculus of the cervical cord, which therefore in reality form a reticulocervical fibre system. The conclusion is reached that the reticulocervical fibre system together with the descending short and long cervicothoracic and cervicolumbar fibres within the intermediate mixed zone of the ventrolateral funiculus of the cord constitute the intermediolateral fascicle of Loewenthal, which is one chain-like descending fibre system within the ventrolateral funiculus.

The controversial opinions about this fibre system and its presumable functional significance are commented upon.


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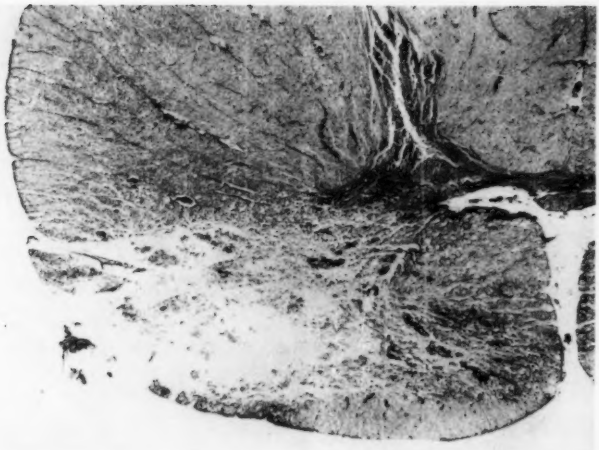

FIG. 7.—Ventrolateral cordotomy at T.4, magnification about × 16.

FIG. 8. FIG. 9.

FIG. 8.—Softening in case VII, magnification × 13.

FIG. 9.—Section of lateral funiculus in low medullary level in case VIII, magnification × 1.

*To illustrate article by Sie Pek Giok.*

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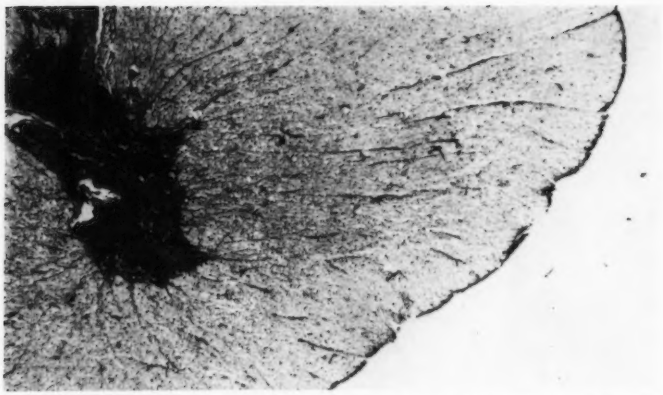

FIG. 10.—Ventrolateral funiculus about 1 cm. caudally to the ventrolateral cordotomy, magnification about ×16.

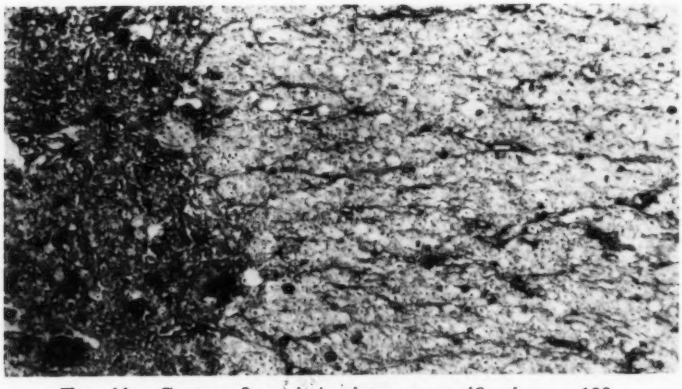

FIG. 11.—Centre of previous picture, magnification × 120.

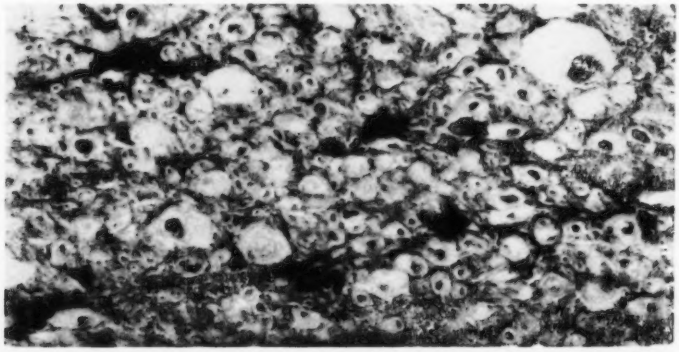

FIG. 12.—Centre of previous picture, magnification × 400, degenerated fibres are seen in large numbers.
All preparations are stained with Häggqvist's method.

*To illustrate article by Sie Pek Giok.*

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# THE MEANING OF "POSTULATIONAL PSYCHO-PHYSICAL PARALLELISM"

BY

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OUR consciousness, on the basis of reasonable inferences from corroborated evidence, may be considered a function of the brain. The brain, in turn, may be regarded as an object, consisting of matter. The material substratum of the functioning brain is in a labile chemical and physical condition, characterized as the living state, which, however, may still be interpreted as a purely material state.

Although consciousness would thus appear to be the function of a material substratum, all hypotheses aimed at deriving consciousness from material processes, or at conceiving consciousness in terms of material events have been unsuccessful.

In view of these consistent failures, it is evidently of fundamental theoretical importance to clarify the indispensable logical basis, as well as the intrinsic limitations of any attempt to solve the "brain-consciousness problem."

The limitations of any such attempt are very definite. Reverting to the old saw "no matter, never mind," it becomes obvious that, since conceptual matter, or physical events, are abstractions from conscious experience, and thus, as mental symbols, remain manifestations of consciousness, any attempt to derive consciousness from physical processes amounts to the *circulus vitiosus* of defining or explaining consciousness in terms of itself.

Again, it becomes likewise obvious that the physicist, in his attempts to formulate or to define a physical world, merely defines, in terms of consciousness, abstractions derived from (conscious) percepts. Such abstractions, although of undeniable significance, logical consistency, and operational validity, may be characterized as fictions. A fiction, in the aspect under consideration, is the assumption of a logically possible thing as a fact, but with the knowledge that this assumed fact remains a mere presupposition, representing an arbitrary symbol or notation with possible operational validity, or in other words, a model encoding significant relationships. We may thus, by the use of appropriate and logically

consistent fictions, and in essential agreement with Vaihinger's concepts (1911), formulate propositions of the following type: "it is as if . . ."

Because of the intrinsic impossibility to derive consciousness from physical processes, some authors (e.g. Coghill, according to C. J. Herrick, 1956) claim that mentation is not a function in the ordinary physiologic sense. Contingent on how "function in the ordinary physiologic sense" is defined, this claim can be upheld or denied. It can be upheld in so far as mentation, i.e. consciousness cannot be causally derived from postulated physical, i.e. physiologic processes in public physical space-time. It can be denied since there is sufficient conclusive evidence to assume that consciousness, in the manner of a dependent variable, is related to that what can be logically described as physical (physiologic) neural events in the brain, and in this respect represents a function of these latter events. I would thus agree with Herrick (l.c.) that mentation is a vital process, and that as such it should be regarded as a "bodily function."

In a rather lengthy disquistion (Confinia Neurologica 17, Suppl., 1957), I have recently attempted to discuss the relationship of brain and consciousness from the epistemological as well as from the neurological aspect, and to integrate both aspects into a unified presentation.

The resulting formulation shows, in some respects, a certain analogy with the principle of complementarity obtaining in contemporary physics, and elaborated by Bohr (1928). Complementarity in this denotation, and perhaps in a somewhat wider sense, refers to a duality, or possible even to a multiplicity in regard to the relation of experience and theoretical (conceptual) formulation.

Paraphrasing a statement by de Broglie (1947, 1955), complementarity may also be expressed as follows: A single actuality, involving the relationships manifested in conscious experience, can be conceptually represented under two aspects which, at first sight, appear incompatible, although truly never entering in direct conflict. When one of these aspects is asserted, the other vanishes, or at least disappears to an extent just sufficient always to avoid a flagrant contradiction. This complementarity, again, involves a principle of correspondence, likewise formulated by Bohr. In the wider sense, this latter principle postulates a significant relationship between the "laws," that is the orderliness, obtaining in both conceptual aspects.

Thus, on the basis of the only data available to us as sentient beings, I have interpreted the actually experienced world of consciousness (the phenomenal world) as a relation-structure of consciousness-modalities in terms of strict Berkeleian idealism.

On the other hand, since, despite the fleeting, jerky, and discontinuous character of consciousness, consistent continuous orderliness prevails, it appears justified to infer and assume the validity of significant persistent relationships independent of consciousness. Consequently, logical systems

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may be formulated, which deal with pertinent aspects of conscious experience in accordance with postulated fictional relationships independent of consciousness. Such systems, expressed in terms of spatio-temporal events (in public physical space-time) presumed to occur while they are not perceived, represent the foundation of physics and chemistry, as well as of biological and other natural sciences. In the logical notation of such systems, I have interpreted the problem of brain and consciousness (here better : brain and behaviour presumably correlated with consciousness) in terms of strict mechanism.

The designation mechanism or, more specifically, mechanistic neurophysiology is here meant to imply that all neural events, including those presumably correlated with consciousness, could exhaustively be described or defined in terms of physics, chemistry, and mathematics (circuit algebra, communication theory). Moreover, it is postulated that all neural events, including those presumably correlated with consciousness, and, in a wider sense, all aspects of observable animal or human behaviour could, in principle, be modelled or imitated by machines. In other words, any activity that we can specify exactly, in terms of the behaviour to be expected in given circumstances, can in principle be met by an artifact. By a simple logical process any such precisely defined behaviour can be coded into the description of at least one mechanism that will model it (MacKay, 1954). Conversely, models built on the principles of communication and control engineering can be regarded as significantly contributing to an advanced understanding of neural functions.

In order to avoid misunderstandings, it should be emphasized that this description, definition, or modelling of neural events, as far as it concerns neural events presumably correlated with consciousness, eliminates consciousness as an observable state of an observed material structure, although presupposing consciousness of the observer. Such presumptive phenomena of consciousness must remain unobservable, since they cannot occur in the private perceptual space-time system of the observer, nor, *ex hypothesi*, in the conceptual public physical space-time of the adopted logical system. It is thus by no means implied that artifacts, mechanical or electronic brains, and robots, are conscious. On the contrary, it is much more likely that, because of complex hierarchic configurational or gestalt properties, the neural activities correlated with phenomena of consciousness can only be performed by circuits which have all the still incompletely understood attributes of living substance. This latter, in turn, requires specific time and environmental factors for its evolution, and is bound to specific patterns of orderliness, among which are also included relations of magnitude with respect to other structures of the space system. The neural events correlated with consciousness phenomena may have unknown but perhaps potentially definable intrinsic gestalt attributes which engineering models built of hardware cannot manifest.

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Yet, there is no way whatsoever to disprove or to prove, in strictly rigorous fashion, whether machines are or are not conscious. An amusing as well as instructive series of highly relevant and clever arguments on this subject can be found in "The Book of the Machines," which is a treatise included (as Chapters 23–25) in Samuel Butler's Erewhon (1872, 1901).

Our philosophical or scientific argumentation, modelling an orderliness independent of consciousness, but related to our given conscious experiences, that is the logical system here under consideration or, in other words, our assumed universe of discourse (Boole, 1854), implies consciousness, namely the consciousness of the reasoner. It is thus not possible, within this universe of discourse, to substitute a conscious observer (or conscious reasoner) by an unconscious registering device (or computing device, or both), and we must clearly distinguish between observation and registration. Such a device, be it ever so complex, is not an observer or reasoner in the terminology of our argumentation. All data, either raw or already mathematically processed (computed or coded), obtained by such devices, remain entirely devoid of meaning until properly expressed, or assumed to be so expressed, in the symbolism of the logical system implying consciousness, that is, until significantly experienced by the observer or reasoner. Moreover, such a device represents an intricate and reasoned artifact, implying purpose, and thus consciousness of the designer and user.

It is here of particular import to eliminate ambiguities with regard to the concepts "real" and "reality"; these terms were clearly defined by Schopenhauer. Adapting a more recent, but essentially identical definition by Bertrand Russell (1948), "real" and "reality" will be used with two distinct denotations: (1) a thing is real when it persists or exists at times when it is not perceived (reality in the first sense); (2) a thing is real when it is correlated with other things in a way which experience has led us to expect (reality in the second sense).

We may now revert to the rather vague but nevertheless useful term matter, which evidently has various different denotations and connotations. The well localized, spatially configurated modalities of consciousness, including many of their reciprocal relationships, are rather easily although not accurately or rigorously symbolized and identified by the concepts of objects, matter, and material events. However, all these experienced material processes represent percepts, occur in private perceptual space-time, and are thus mental. Yet, we might designate such objects or processes as perceptual matter. Nevertheless, some such material processes are poorly localized and not spatially configurated, e.g. odours and sounds. No definite demarcation can be drawn between such perceptual material processes and the poorly localized, spatially not configurated consciousness-modalities represented by vague feelings, emotions and thoughts, i.e. by mind *sensu strictiori.*

We postulate now that, independent of our consciousness, and in a

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persistent public physical space-time, configurated events take place, which are, at least in certain respects, topologically similar to our experienced perceptual material processes in private perceptual space-time. These postulated events in public physical space-time represent conceptual matter, that is the physical world. These conceptual physicalisms remain nevertheless mental abstracta, or "*illata*" in positivistic terminology.

Whitehead (1948) claims that each event has a character of its own which is analysable into two components: first, there are the objects situated in that event; and second, there is "the field of activity of the event which regulates the transference of the objects situated in it to situations in subsequent events. It is essential to grasp the distinction between an object and an event. An object is some entity which we can recognize, and meet again; an event passes and is gone". I deny the validity of this distinction. An object is a recognizable pattern of percepts in perceptual space-time, and such recognizable pattern is an event which "passes and is gone". At most, we can and do, in everyday speech, use the expression "object" for relatively stable patterns of spatially configurated public data. In the assumed physical space-time, there are no objects, only conceptual events, some of which can be conceived as magnitudes. If these magnitudes are regarded as "objects," then they become hypostatized, and we have here a μετάβασις εἰς ἄλλο γένος. Bertrand Russell (1945) emphasizes that in contemporary physics distance is between events, not between things, and involves time as well as space; thus, in modern physics, there is no action at a distance.

The postulated physical events, inferred on the basis of observed. i.e. experienced mental events (percepts), may be assumed to consist of movable magnitudes and magnitudes of motions. Some of these events may be assumed to have properties definable as mass (i.e. be ponderable), and others may be assumed to have properties definable as energy, the two being convertible into each other. Again, some of the postulated events may be assumed to have properties definable in terms of field effects.

It is obvious that the difference between mass and energy is an important basic distinction and there is no inconvenience in speaking of mass and energy instead of matter and energy. Matter is the more vague term, which might be qualified as matter *sensu latiori* (physicalisms), and matter *sensu strictiori* ("ponderable matter", mass). Loosely speaking, one is inclined to use the word matter in either connotation.

Eliminating the so-called secondary qualities, a four-dimensional physical world based upon the primary qualities is thus postulated; it is assumed, *ex hypothesi*, that this physical world is real in the first sense, and moreover, by definition, stripped of all attributes of consciousness.

It seems evident, however, that this assumed "physical reality", based upon the concept of a physical space-time system, is a fiction. Consciousness, which represents the only set of data given to us as sentient, perceiving,

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thinking and emotional beings, is a fleeting phenomenon with many jerky manifestations, often instantaneously changing in the manner of step-functions, and characterized as an individual, private perceptual space-time system which completely disappears and reappears. Consciousness or mind *sensu completo* is thus light or dark, purple, green or red, etc., odorous, hard, soft, heavy or light, warm, cold, loud or silent, pleasant or unpleasant, and at times cogitating. It consists of spatially configurated events (shapes) or of amorphous masses, of patterns, feelings, emotions or thoughts—these latter, although vaguely localized, have some of the intangible shadowy aspects characteristic e.g. for odours. All these phenomena fill out or comprise a transitory ameboid individual perceptual space-time system. These data are thus not real in the first sense according to the postulated premiss.

Since significant orderliness seems to persist independently of any percepts in the widest sense, that is independently of, or without consciousness, we may postulate, as stated above, an independent reality in the first sense. The assumption of what some authors choose to call a dichotomy between consciousness (mind) and reality is thus, I believe, self-evident and unavoidable.

However, this reality, being independent or devoid of the attributes of consciousness, could not be defined in terms of consciousness-modalities. It would be neither coloured, nor light, nor dark, nor loud, nor silent, nor pleasant, nor unpleasant, nor painful etc. In other words, we could only express it in terms of extreme abstractness. We have so far eliminated all the so-called secondary qualities, and we might then believe that we could, *ex hypothesi*, express reality in terms of orderly events involving the primary qualities. But this belief is a delusion: the primary qualities are merely abstract notions of perceptual space-time relationships, and perceptual space-time, in turn, represents the substratum of consciousness. It follows that we can only express reality by the ultimate abstraction of an orderliness x. Whatever persists beyond consciousness must thus be regarded as inexpressible, undefinable and unknowable. Even the very word "persists" becomes meaningless, since reality, beyond the domain of space-time relationships, cannot be conceived in any temporal term such as duration or "events." This reality x, devoid of any expressible particularity, cannot be brought in meaningful relation to particular events in consciousness.

David Hume (1748), in his Essay XII, of the Academic or Sceptical Philosophy, clearly recognized the cogency of the argument denying the intrinsic difference between secondary and primary qualities. The relevant passage in Hume's Essay states: " 'Tis universally allowed by modern enquirers, that all the sensible qualities of objects, such as hard, soft, hot, cold, white, black, etc., are merely secondary and exist not in the objects themselves, but are perceptions of the mind, without any external

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archetype or model which they represent. If this be allowed, with regard to secondary qualities, it must also follow with regard to the supposed primary qualities of extension and solidity; nor can the latter be any more entitled to that denomination than the former. The idea of extension is entirely acquired from the senses of sight and feeling; and if all the qualities, perceived by the senses, be in the mind not in the object, the same conclusion must reach the idea of extension, which is wholly dependent on the sensible ideas or the ideas of secondary qualities."

Whitehead (1948) justly remarks that this argumentation may have been one of the various reasonings of Hume that influenced Kant. Furthermore, seen from another viewpoint, Hume's argumentation is perfectly consistent with George Berkeley's fundamental views.

Moreover, Whitehead (l.c.) takes up the same argument, yet without consistently following it through to its unavoidable conclusion. Whitehead quotes Hume's statement and adds that, since space and time cannot be disjoined "not only must perceived space, but also perceived time, be considered as mental and purely personal to each individual. But we have agreed that all our knowledge is based on experience. We are thus led to the conclusion that all our knowledge is the play of our own mind. Indeed, on this supposition, it is a mere silly trick which leads me to speak in the plural, and I cannot imagine how I acquired the habit. For I have no source of information to give me news of anything beyond myself. The space-time of science is thus absolutely swept away."

Whitehead then repudiates the idealistic view with a series of cryptic arguments: "My own position is that consciousness is a factor within fact and involves its knowledge. Thus apprehended nature is involved in our consciousness. But in its exhibition of its character our consciousness exhibits its significance of factors of facts beyond itself."

Reverting to the legitimate and in fact inescapable conclusion that "the space-time of science" (i.e. the public physical space-time) "is absolutely swept away," I deny that it is "a mere silly trick" to assume other sentient beings, allegedly because "I have no source of information to give me news of anything beyond myself." The legitimate source of information is the principle of sufficient reason, which justifies, as I shall attempt to show below, the assumption of other similar sentient beings, or consciousness-manifolds. Again, we may assume that our consciousness-manifolds are manifestations of a consistent orderliness. This means, in other words, that our world is rational (Whittaker, 1948). Or we may assume that consistent orderliness does not obtain, and that our world is irrational. But then, it could not be modelled in rational thoughts, and we should give up any such attempt. Assuming that our world is rational, we must presuppose the consistent validity of the relationship "if . . . then . . . " which is a concise formulation or definition of the principle of sufficient reason, which, again, implies the principles of identity and con-

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tradiction, as well as the possibility of induction. Without the principle of sufficient reason, science is impossible.

Now, as regards Whitehead's further statements, it seems justifiable to say that "our consciousness exhibits its significance of factors of facts beyond itself", but this statement cannot logically imply anything more than the independent existence of an unqualifiable orderliness x representing reality. In so far as relationships between different consciousness-manifolds are involved, the significance of factors of facts beyond any one consciousness-manifold could be said to correspond to the orderliness expressed by the concept of public data, which I have discussed in my monograph (K., 1957).

We may also formulate the two theoretically basic problems, first that of the existence of other sentient beings, and second that of the reality x, as follows:

(1) A consciousness-manifold, which shall be designated as my consciousness-manifold, has its centre of reference in localized and spatially configurated consciousness-modalities representing my body including my brain. It appears logically permissible to assume that similar consciousness-manifolds, characterized by their individual space-time systems are, under similar functional conditions, similarly related to similar other bodies and brains which I experience as extraneous to my own body and brain. In other words, and following the principle of sufficient reason, I define inferred other consciousness, not my own, in terms of my own consciousness.

(2) It appears to me, however, highly illogical, and inconsistent with the principle of sufficient reason, to qualify and define a reality which, by definition, is assumed to exist when there is no consciousness, in terms of consciousness. If such a reality exists, it is, by definition, not consciousness. But when there is no consciousness, and since consciousness cannot be conceived as anything else that the manifestation of some of its essential properties, it is illogical to attribute any of these same essential properties to a reality which is not consciousness.

As regards these problems, we are obviously in a difficult predicament, from which, on purely logical grounds, there seems to be no escape whatsoever. This predicament may be succinctly expressed as the brain paradox, based on Schopenhauer's formulation: our phenomenal world of consciousness is a brain phenomenon, but the brain itself, as we know it, is a phenomenon of consciousness; or, in shorter form: consciousness is a brain phenomenon, but the brain itself is a brain phenomenon.

For practical purposes, both the neurologist and the physicist, who deal with fundamental concepts concerning the structure of our world, must assume a physical reality in the second sense. Einstein (1934) has justly remarked that since "sense perception only gives information of this external world or of 'physical reality' indirectly, we can only grasp the

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latter by speculative means. It follows from this fact that our notions of physical reality can never be final."

Planck (1931) has formulated two so-called fundamental canons of natural philosophy as follows:

(1) There is a real outer world which exists independently of our act of knowing.

(2) The real outer world is not directly knowable.

My own formulation (K., 1957) is slightly different and can be condensed in the following two sentences:

(1) There is a real orderliness x independent of (my or our) consciousness.

(2) This independent reality is both transcendental and transcendent. It remains therefore unknowable.

I believe that the first of these statements can be proved as far as "my consciousness" is concerned, if I accept the principle of sufficient reason, that is, if I admit at all the possibility of proof. The necessary assumption of the real orderliness x rests upon the fact that, despite disruption in and discontinuity of my consciousness, continuous orderliness prevails. Again, following the principle of sufficient reason, I may infer that other similar consciousness-manifolds exist, and thus, although strict or dogmatic solipsism cannot be disproved (nor proved) by rigorous proof, such solipsism seems less reasonable than the assumption of other sentient beings, and contradicts the principle of specification: *entium varietates non temere esse minuendas*. This principle is the converse of Occam's (Ockham's) razor.

Now, as regards the second statement, the qualification transcendental, used in Kant's strict sense, simply means that the orderliness x is intelligible (or in other words apprehensible by thought) as a necessary condition without which the orderliness of consciousness would be impossible. The qualification transcendent means that the orderliness x, stripped of all attributes of consciousness, is propertyless and qualityless. It is therefore beyond the substratum of our senses (mind *sensu latiori*) and of our thoughts (mind *sensu strictiori*). One might thus say that the orderliness x would be nothing at all, were it not intelligible as abstract transcendental orderliness. We might also use the term transcendent as synonymous with metaphysical. Beyond the necessary assumption of the real orderliness x there is no way whatsoever to qualify this ultimate abstraction and all the efforts of metaphysicians to obtain knowledge of reality must be considered intrinsically vain. Since, however, the orderliness x can be apprehended as necessary by thought, it can also be apprehended as a feeling or emotion, that is by affectivity. This approach to reality is that of the mystic. Although this approach has its justification, its domain remains, in my opinion, almost entirely outside the domain of rational scientific thought. Moreover, I believe that the mystics are erroneous in

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claiming direct and emotionally qualifiable apprehension of the orderliness x. Mysticism, at best, can give a relatively valid emotional interpretation of the world of consciousness with respect to the orderliness x, but not of that orderliness itself, which has neither logically nor emotionally expressible qualities, properties, or particularities.

It can thus be seen that we are compelled to use the terms to "be" or to "exist" with two fundamentally different denotations, namely as essentially qualifiable, expressible, knowable phenomenal existence, and as intrinsically non-qualifiable, unknowable metaphysical existence.

In the ordinary sense, only phenomenal existence can have any meaning for us as sentient beings. The verbs to be or to exist simply denote here the occurrence of an event in private perceptual space-time: *esse est percipi, et percipi est esse*. An event occurs when it is perceived; conversely, when an event is perceived, it occurs. We can, of course, imagine an unperceived event as occurring or having occurred, but then we "perceive" it as modelled by occurring thoughts.

Clearly, a thought exists only while it is conceived, i.e. "perceived" as a thought. Again, logical and mathematical existence can be defined as a special form of thought-existence, namely a thought-existence free of contradiction, or thought-existence *sensu strictiori*. Thought-existence *per se* (or *sensu latiori*) does by no means imply freedom from contradiction. Boole's laws of thought (1854) obviously refer to thought *sensu strictiori*.

To state that "there are multiplication sums which no one will ever have worked out" (Russell, 1945) means merely that we are creating, in thoughts, abstract, undetermined multiplication sums involving less abstract, i.e. more concrete possibilities which, as we suppose, will never be actualized in, or created by, thoughts. These multiplication sums have as much or as little existence as unspecified children that, in our imagination, could be born next year, but will not be born. To attribute any other "real" existence to such sums or such children is, in my opinion, an illegitimate hypostatization.

It should moreover be stressed that purpose, affectivity (emotion), and axiologic value are very significant aspects of thought as well as, generally speaking, of our world of consciousness. But these aspects, which I have discussed in my monograph (1957), are not included in the topic here under consideration.

Because the metaphysical reality x remains inexpressible for a sentient being such as man, the fictitious concept of public physical space-time and of physical events must be considered a convenient logical and mathematical notation for a description and interpretation of postulated events occurring independently of consciousness but expressible in the symbolism of consciousness. Postulational psycho-physical parallelism may accordingly provide a useful working hypothesis correlating, not by a causal, but



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by a logical transposition, the orderliness obtaining in the assumed physical world with the orderly sequence of the events in consciousness.

Ashby (1956), using the lately reintroduced designation "cybernetics," has recently elaborated an interesting theory of transformations which can be applied to a discussion of the referred logical transposition. Adapting the concepts of R-events and N-events, as defined in my monograph (1957), to Ashby's terminology, we have a set of operands, namely the R-events, transformed by an operator, namely the neurosensory mechanisms. The R-events, representing physical events, are thus changed, in this sense by a closed transformation (which creates no new element), into N-events (i.e. other physical events). In another sense, since the N-events, as coded signals, differ from the R-events, the transformation can, of course, also be defined as open, but this, again, depends on how we define the operands. After a series of closed transformations by the neural mechanisms, which represent in this respect a true transducer, namely a machine with input, we have, at a certain level, another type of transition, namely an essentially two-valued transformation. One of these transformations remains closed in the adopted sense. The other transformation is open, creating a new element, namely events in perceptual space-time, that is conscious events. The parameter of the closed transformations is public physical space-time, the parameter of the open transformation is private perceptual space-time.

In abbreviated as well as oversimplified form, and adapting Ashby's procedure, the transformations could be expressed by a matrix in the following manner:

| $\downarrow$ | $r_1$ | $r_2$ | $r_3$ | $r_4$ |
|---|---|---|---|---|
| $T_x$ | $n_1$ | $n_2$ | $n_3$ | $n_4$ |
| $T_y$ | $P_1$ | $P_2$ | $P_3$ | $P_4$ |

where r signifies R-event, n stands for N-event, and P denotes the parallel event of consciousness. T designates the transformation; T's subscript x represents the parameter "physical space-time," and the subscript y stands for the parameter "perceptual space-time". There are, of course, a number of successive transformations $T_x$, such as $T_{x_1}$, $T_{x_2}$ . . . etc. Adapting Ashby's method of kinematic graphs of transformations, we could also use the form

$$r_1 \rightarrow n_1 \rightarrow n_{1'} \rightarrow n_{1''} \rightarrow n_{1'''} \rightarrow r'.$$
$$\vdots$$
$$\downarrow$$
$$P_1$$

This kinematic graph as well as the preceding matrix represent, of course, crude oversimplifications, merely meant to model a particular aspect of the problem under discussion.

Concerning parallelism, it must be emphasized that the "transforma-

tion" or "transition" from physical N-events to parallel events of consciousness is a purely logical transformation, not involving interaction. Since physical events and mental events occur in different space-time systems which have no dimensions in common, no path, course, direction, trajectory, velocity or motion could lead, in a given time, from one system into the other. The transformation (if this term is used) is therefore instantaneous, or rather, does not involve distance and time at all. There is thus no causal connection between the two series of events, since the concept of causal relationship, as defined by Schopenhauer and adopted in my monograph, implies interaction, namely changing events involving a given time, and following the principle of mass-energy conservation. The two series of events are, strictly speaking, neither spatially parallel nor temporally simultaneous, although the parallel events of consciousness may be conceived "as if" simultaneous with certain still insufficiently definable cortico-thalamic N-events. Nevertheless, in order to avoid undue pedantry, we may accept the term "parallel" in the wider sense or as a figure of speech.

Again, assuming "simultaneity" of parallel consciousness-events and parallel physical N-events, perceptual time necessarily lags behind the assumed public physical time, as far as the pattern of experienced R-events is concerned. We have here, in addition to velocity-differences related to the R-events concerned (e.g. light and sound), various delays related to neural processes, such as velocities of conduction and synaptic delays.[1] These lags, even with respect to the purely neural processes (i.e. N-events), may noticeably differ as regards for instance optic, acoustic, and tactile neural events related to one and the same group of "external events" (R-events).

Simultaneity in the public physical space-time system has proved to be an exceedingly difficult problem, which was particularly stressed by Einstein, who proposed a practical solution based on an arbitrary convention. We cannot fix the time "of an event whose distance from the clock is not negligible; for there are no 'instantaneous signals' that we can use in order to compare the time of an event with that of the clock"

[1]The relation between sense-experience (consciousness-events in private perceptual space-time) and the physical as well as physiologic processes (events in public physical space-time) involved in perception has been recently discussed by J. R. Smythies in his important contribution "Analysis of Perception" (1956). Smythies justly points out the salient internal inconsistencies in the ordinary scientific but naïve account of perception. Discounting some differences in terminology, approach and evaluation, Smythies' argumentation is to a certain extent very similar to my own. This is particularly significant, since we proceeded along different lines and were entirely unacquainted with each other's work. I refer specifically to Smythies' Theory I in which this author states: "We can understand that the Universe may be composed of a great number of three-dimensional spatial systems (or four-dimensional spatio-temporal systems) none of which bear any spatial relations to any of the others." This, again, is also exactly my viewpoint.

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(Einstein, 1945). Questions of simultaneity assume considerable importance, if a value of t must be assigned to two physical systems moving with respect to each other in some reference system.

Simultaneity with respect to two different perceptual space-time systems is, depending on the viewpoint, either meaningless or a fictional practical approximation with considerable uncertainty. It can be expressed as follows: a pattern of experienced compresent events in the observer's consciousness may be conceptually related to inferred simultaneous parallel N-events in a postulated physical space-time system. Within that latter system, the parallel physical N-events are causally related to antecedent other (non-parallel) N-events which, again, are causally related to antecedent R-events. These R-events, in turn, may be assumed to be related, *mutatis mutandis*, and with a corresponding time lag, to events in the inferred consciousness-manifold of the observed sentient being. This latter pattern of events can be regarded, depending on the circumstances, and with due consideration of the involved probable conceptual time equations, as an approximately simultaneous transformation of the pattern experienced by the observer. It is of interest to note that this simultaneity involves a negative as well as a positive value of t.

In abbreviated and elementary form, where P signifies the perceptual (parallel) event, ob the observer, os the observed sentient being, t′ the perceptual time, t the physical time, $t_n$ the physical time of neural delay, and R the R-event, this approximate and imaginary simultaneity could be expressed as follows:

$$P_{ob}\ (t') - t_{nob} = R(t)$$
$$R\quad (t) + t_{nos} = P_{os}(t')$$

now (assuming simultaneous R-events at the neurosensory level), if

$$t_{nob} = t_{nos} \qquad \text{then} \qquad P_{ob}(t') = P_{os}(t').$$

Temporal continuity of a given neurosensory "machine", pertaining to a given individual organism in public physical space-time, is provided by the continuity of a significantly persisting morphologic pattern throughout all changes of metabolism and turnover of labile histologic elements. The perennial histologic elements constitute relatively enduring spatio-temporal patterns. Moreover, engraphy (Semon, 1904; Forel, 1922; K., 1957) represents here an important factor. In private perceptual space-time, temporal continuity or identity throughout a succession of constantly changing patterns, including interruptions by complete disappearance of the entire consciousness-manifold, followed by reappearance, is provided by memory. The concept of parallelism relates memory phenomena to the activation of engrams. Again, as regards the logical transposition from physical N-events to parallel events of consciousness, this transformation might simply be expressed as follows: a certain discharge-configuration of cortico-thalamic neural circuits in public physical space-time means (or signifies), say, a panoramic mountain-

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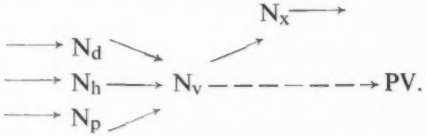
landscape extending, in private perceptual space-time, through my (or *mutatis mutandis* someone's) visual field. It is here, moreover, essentially irrelevant whether this landscape is dreamt, hallucinated, or actually observed. In all three cases it is "perceived" or it "occurs." The referred significant configuration or pattern of cortico-thalamic N-events (presumably involving the occipital cortex) represents, in Ashby's terminology, a transform which does not indicate a unique operand. On the other hand, the referred cortico-thalamic pattern constitutes itself an operand which, as regards the open one of its two (or more) transformations, is itself unique. This could be expressed as follows:




The N-events are here indicated by N. The subscripts, d, h, p specify three different operands, namely (non-parallel) N-events occurring in dreams, hallucinations, and normal perception, respectively. It is assumed that only one of these three patterns of events occurs at one given time. The subscript v indicates the physical parallel N-events corresponding to the referred mental visual parallel events PV. The arrow with broken line symbolizes the open (or in Ashby's terminology "unclosed") transformation. The subscript x indicates the physical N-events to which the operand $N_v$ is changed by closed transformation. Both transformations of $N_v$ are simultaneous. The open transformation (from public physical space-time to private perceptual space-time) is considered "instantaneous" and unique. The closed transformation takes place in physical space-time, is not necessarily single-valued, and involves the physical time related to conduction velocities and synaptic delays.

In addition to the postulated set of transformations or transitions from events in fictional public physical space-time to events in private perceptual space-time, there is, of course, still another, and I believe, almost self-evident "psycho-psychical" parallelism which can be expressed as follows. If I deal with, and observe another presumably conscious person, I infer, from my experiences and my cogitations, another "parallel" private perceptual four-dimensional space-time manifold which is functionally related to a limited region of my own private perceptual space-time, namely to the region manifested by my percepts of the observed person's head. This inferred perceptual space-time manifold involves another set of four dimensions, and is extraneous to my own. It evidently cannot be located in my own space-time manifold. Yet, it "duplicates" or "parallels," in transposed form, and in another set of dimensions, many of the events occurring in my own manifold. Moreover, even if I must regard the observed person's head as a "black box" (presumably containing a

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brain), the inferred "parallel" perceptual space-time system depends on certain states which involve my actual (as well as potential) percepts. In fact, the observer, if a neurosurgeon or neurologist attending a brain operation under local anæsthesia, could talk with the observed patient while perceiving and testing that patient's brain. In this sense, we have an ill-defined transformation of operands from one perceptual space-time system into the other. Ignoring the inferred physical events, this transformation could be said to correspond to the formulation

$$P_{ob}(t') = P_{os}(t')$$

discussed above.

Russell (1945), in perhaps justly criticizing various concepts of Bergson, states that "the brain, which nobody sees, is not, in the ordinary sense, an image." I believe, however, that this statement is unjustified. Surely, to the competent neurologist, the brain, living and dead, is frequently a percept, directly or indirectly, and through various senses. It is, moreover, for such neurologist, a very significant complex of concepts or mental (*sensu strictiori*) images, which direct, or program, his inferences. The brain is thus, under such circumstances, very definitely an "image."

As regards the interpretation of the brain paradox with reference to "my own" or "one's own" brain, the following statement could be made. My visual percept of a distant panorama is related, in an orderly fashion, to my visual, tactile, and proprioceptive percepts of my own head, containing a brain which I actually perceive through proprioception by its weight. Although the detailed image of my brain is conceptual, that brain could, under very unusual circumstances, become for me a brain perceived by other senses besides proprioception.

The cited relationship is now such that, if certain conceivable and in part potentially perceivable events occur within my private perceptual space-time system, i.e. consciousness-manifold, and with respect to that brain which is part of the system, then the manifestation or percept of that distant panorama, or, for that matter, all visual percepts would vanish. If certain other conceivable and at least in part potentially perceivable events would take place in my consciousness-manifold and with respect to my conceptual (or potentially perceivable) brain, then my entire consciousness-manifold would either temporarily or permanently vanish.

This, of course, is a rather poor sort of formulation, and not particularly convenient as a basis for scientific knowledge or explanation. But I would maintain that it is the best we can do on the basis of the idealistic approach which, although—as I believe—logically unassailable, is poorly suited to the practical demands of neurologic theory.

To summarize: we may describe our experiences in terms of what we actually experience, namely in terms of percepts, feelings, thoughts, and voluntary activity. This, by definition, is consciousness, taken as synonymous with mind.

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Or we may describe our experiences in terms of inferred physical events, conceived as related, or corresponding, to our experiences, and postulated to occur independently of being perceived. This, by definition, implies matter in the physical sense.

Now, if we start with matter, there is no mind, and if we start with mind, there is no matter. Closer analysis shows that the concept of matter and physicalisms has an inherent weakness, since it implies, in the last end, the occurrence of percepts without being perceived, or of experiences that are not experienced, or, again, of conceivable concepts "existing" without being conceived; it is, moreover, based on a *petitio principii*. The concept of mind is logically stronger, but unsuited for the practical descriptions and the theories of natural sciences.

We may thus combine the use of the two concepts by a postulate of logical psycho-physical parallelism, regarded as an artificial auxiliary construction. This construction might be called a subterfuge, but, if its artificial nature "as if" is stressed, and since no attempt at concealment is made, the term "subterfuge" applies as little to this construction as the term "lie" applies to an avowed fiction. There is, of course, no psycho-physical parallelism except as a system of thoughts, because there are no physicalisms, except in our imagination.

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# NOTICES OF RECENT PUBLICATIONS

## INFORMATION THEORY AND THE NERVOUS SYSTEM

*The Physical Foundation of Biology. An Analytical Study.* By WALTER M. ELSASSER, Professor of Theoretical Physics, University of California. La Jolla. Pergamon Press, London, New York, Paris, Los Angeles. Pp. 219. Price 30s.

This book is an analysis of the relationship of biology to physics in the light of current physical theory, and a discussion of the possible applications of modern information theory to certain biological phenomena which have hitherto resisted interpretation on mechanistic lines. The author is careful to explain at the outset that this does not mean that he is on the side of the vitalists. He considers that they were wrong in three respects. In the first place they identified their non-physical principle largely with purposeful action, which he maintains we now know can be expressed by means of purely mechanistic devices. In the second place they failed to emphasize the quantitative character of all scientific description, and, lastly, they neglected the logical analysis which becomes indispensable when one claims that physics and chemistry are inadequate.

Roughly the first half of the book is devoted to a description of the physical devices by which information can be stored, and problems solved, on a scale, and with a speed, hitherto inconceivable. This leads to a consideration of the two main biological functions which depend upon the storage and subsequent availability of "information." These are memory, and embryological development. The latter in terms of information theory is held to be the outcome of a vast number of items of information stored in the genes, and determining the growth and development of the organism. In the old controversy between the preformationists and the epigeneticists the epigeneticists were right, but the problem is to explain how the information is stored in the genes.

Professor Elsasser reaches the conclusion that in order to describe both memory and embryological development it is necessary to make use of fresh concepts, which cannot be described in mechanistic terms. The maintenance of information during the life-span of an organism, he says, is mainly "biotonic." This does not mean that it does not obey the causal laws of physics, but that owing to the ultra-microscopic size, and enormous numbers of the units involved, it is not possible, as it is in classical physics, to make the observations which would result in the discovery of the mechanistic laws. "The formal laws describing organic, and in this case cerebral, behaviour cannot be reduced to the conceptual and mathematical scheme of classical physics." Nevertheless Professor Elsasser believes that the storage of both genetic and mnemic information must take place through modifications in the structure of molecules, and he shows that on the analogy of electronic computers there is plenty of room in the molecule for this purpose. "In the language of information theory, the appearance of biotonic modes of behaviour depends on internal inputs that supply,

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out of an immense reservoir, messages whose individual character is withdrawn from direct observation."

Professor Elsasser is careful to stress that the detailed biological applications of his theory lie outside his sphere. He does not tell us how the information is coded into the molecule, nor how it becomes available again embryologically in the form of the shape of a limb, or psychologically in the memory of a visual scene. The neurologist will wonder how the information with which he is familiar in terms of impulses occurring in an anatomical arrangement of neurones of specific pattern, e.g. in the visual cortex, are translated into patterns of molecular structure. Whether or not Professor Elsasser is right, those who are interested in the no-man's-land between physics and neurology will find his book a stimulating one.

RUSSELL BRAIN.

## NEUROPATHOLOGY

*Neuropathology*. By J. G. GREENFIELD, W. BLACKWOOD, W. H. MCMENEMEY, A. MEYER and R. M. NORMAN. 1958. Pp. 640. London: Edward Arnold Ltd. Price £5 5s.

Dr. Greenfield's *Neuropathology* was published just after he died although he saw it in page proof. It has been eagerly awaited as the main result of his work in the years after he had retired from the staff of the National Hospital, Queen Square. All his professional life had been spent in observation and personal teaching. It is difficult to realize when considering his place in neuropathology and when reviewing his many original papers (notably in *Brain*) that he worked as a hospital pathologist, spending his days in routine duties, and that the bulk of his observations and comments are stored in case notes and in the experience of his friends whom he advised and taught. His teaching was very personal and he had never formally recorded his great experience and knowledge. The opportunity to encourage him to do this by writing a textbook of neuropathology came with his retirement from the National Hospital, but when he was freed from routine work he became even more active in investigation and personal teaching, and the text had to take second place. Fortunately, he worked steadily at it for some years and delegated some of the work, as the title shows.

Dr. Greenfield's close colleagues helped with chapters on their special subjects—Professor Blackwood on vascular disease; Professor Alfred Meyer with one on anoxias, intoxications and metabolic disorders, and one each on epilepsy and the psychoses; Dr. McMenemey on dementias and progressive diseases of the basal ganglia; and Dr. Norman on malformations, birth injury and diseases of early life. Each of these chapters is by a man writing upon a subject with which he is identified, and none needs any introduction or comment.

Although there are five contributors, Dr. Greenfield was by far the major, with nearly half the book—in pages or chapters—from his pen, so that naturally to associate it with his name has factual support.

The only comment which need be made upon the text in this Journal has been made in the preface—"As the large subject of cerebral and spinal tumours is treated in a companion volume edited by Professor Dorothy S. Russell, it is omitted from this book."

The volume is a landmark in English neurological teaching.

DENIS WILLIAMS.



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## SHORTER NOTICES

*The Cerebrospinal Fluid.* Ciba Foundation Symposium. Edited by G. E. W. WOLSTENHOLME, O.B.E., and CECILIA M. O'CONNOR. 1958. Pp. 335. London: Churchill. Price 50s.

This latest addition to the volumes of essays based on papers given at the Ciba Symposium has exactly the same format as others of the series. It is only necessary to bring its publication to the notice of readers of *Brain*, for the 25 contributors, under the chairmanship of Professor Mitchell of Manchester, are all well known. The range of discussion is very wide. It includes description of tissue culture of the choroid plexus by Professor Lumsden, of mechanical aspects of the circulation by Mr. Norman Dott and Mr. Gillingham, and a number of biochemical and pathological papers.

This short notice gives us the opportunity to be grateful to the Ciba Foundation for the contribution it is making to the background of medicine, in London particularly.

DENIS WILLIAMS.

*Psychopharmacology. Pharmacologic Effects on Behaviour.* Edited by HARRY H. PENNES, M.D., D.Med.Sci.(Neurology), New York Psychiatric Institute, New York. 1958. Pp. 362. London: Cassell & Co. Price 60s.

This volume is third in a series "Progress in Neurobiology." Forty people met in New York to discuss the modes of action of sedatives, tranquillizers and hallucinogens. Their conference is summarized in 13 papers on biochemical, physiological, theoretical and behavioural aspects of their subject, which has occupied psychiatrists so much in the past ten years. Its title seems a pity.

*Elektroencephalographische Studien bei Hirntumoren.* By Dr. med. RUDOLF HESS, Zurich. 1958. Pp. 138. Stuttgart: Georg Thieme Verlag. Price DM. 19.80.

This is a statistical correlation between electro-encephalographic changes and tumour characteristics. It is based on all the work done in Professor Krayenbuhl's clinic in seven years, and is a concise and valuable survey. Of particular interest is the study of changes in the electro-encephalogram with increasing depth of the tumour within the hemisphere.

*Die Kausalgie ein Beitrag zur Frage der Schmerzen bei Peripheren Nervenverletzungen.* By E. TROSTDORF. 1956. Pp. 138. Stuttgart: Georg Thieme Verlag. Price DM. 10.50.

This book adds nothing to what is already known about causalgia. It simply reviews the known facts and adds 187 new cases due to war wounds, 60 of which were subjected to detailed sensory studies.

*The Selected Writings of John Hughlings Jackson*, Vol. 1. *On Epilepsy and Epileptiform Convulsions.* Vol. 2, *Evolution and Dissolution of the Nervous System. Speech, Various Papers, Addresses and Lectures.* Edited for the Guarantors of Brain by JAMES TAYLOR, M.D., F.R.C.P., with the advice and assistance of GORDON HOLMES, M.D., F.R.C.P. and F. M. R. WALSHE, M.D., F.R.C.P. New York: Basic Books, Inc. $15 the set.

Since these two volumes of Hughlings Jackson's Selected Writings have long been out of print their republication in a form which is an exact reproduction of the original volumes is very welcome.

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